concerning the SAB can be found on the SAB Home Page at: http://www.epa.gov/sab.

Dated: August 12, 1998.

Patricia Thomas,

Acting Staff Director, Science Advisory Board.

[FR Doc. 98–22318 Filed 8–18–98; 8:45 am]

BILLING CODE 6560–50–P

ENVIRONMENTAL PROTECTION AGENCY

[PF–821; FRL–6019–6]

Rohm and Haas Company; Pesticide Tolerance Petition Filing

AGENCY: Environmental Protection Agency (EPA).

ACTION: Notice.

SUMMARY: This notice announces the filing of pesticide petitions proposing the establishment of a tolerance for residues of a certain pesticide chemical in or on various raw agricultural commodities.

DATES: Comments, identified by the docket control number [PF–821], must be received on or before September 18, 1998.

ADDRESSES: By mail, submit written comments to Information and Records Integrity Branch, Public Information and Services Division (7502C), Office of Pesticide Programs, Environmental Protection Agency, 401 M St. SW., Washington, DC 20460. In person, bring comments to Rm. 119, CM #2. 1921 Jefferson Davis Highway, Arlington, VA.

Comments and data may also be submitted electronically by following the instructions under ''SUPPLEMENTARY INFORMATION.'' No confidential business information should be submitted through e-mail.

Information submitted as a comments concerning this document may be claimed confidential by marking any part or all of that information as ''Confidential Business Information'' (CBI). CBI should not be submitted through e-mail. Information marked as CBI will not be disclosed except in accordance with procedures set forth in 40 CFR part 2. A copy of the comment that does not contain CBI must be submitted for inclusion in the public record. Information not marked confidential may be disclosed publicly by EPA without prior notice. All written comments will be available for public inspection in Rm. 119 at the address given above, from 8:30 a.m. to 4 p.m., Monday through Friday, excluding legal holidays.

FOR FURTHER INFORMATION CONTACT: By mail: Joseph Tavano, Registration Division (7505C), Office of Pesticide Programs, Environmental Protection Agency, 401 M St., SW., Washington, DC 20460. Office location, telephone number, and e-mail address: Rm. 214, CM #2, 1921 Jefferson Davis Highway, Arlington, VA 22202. (703) 305–6411; tavano.joe@epamail.epa.gov.

SUPPLEMENTARY INFORMATION: EPA has received pesticide petitions as follows from Rohm and Haas Company, 100 Independence Mall West, Philadelphia, PA. 19106–2399, proposing pursuant to section 408(d) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. 346a(d), to amend 40 CFR 180.472 by establishing a tolerance for residues of tebufenozide [benzoic acid, 3,5-dimethyl-, 1–(1,1-dimethylethyl)-2–(4-ethylbenzoyl) hydrazide in or on various raw agricultural commodities. EPA has determined that these petitions contain data or information regarding the elements set forth in section 408(d)(2) of the FFDCA; however, EPA has not fully evaluated the sufficiency of the submitted data at this time or whether the data supports granting of the petition. Additional data may be needed before EPA rules on the petition.

The official record for this notice, as well as the public version, has been established for this notice of filing under docket control number PF–821 (including comments and data submitted electronically as described below). A public version of this record, including printed, paper versions of electronic comments, which does not include any information claimed as CBI, is available for inspection from 8:30 a.m. to 4 p.m., Monday through Friday, excluding legal holidays. The official record is located at the address in ''ADDRESSES'' at the beginning of this document.

Electronic comments can be sent directly to EPA at:

opp-docket@epamail.epa.gov

Electronic comments must be submitted as an ASCII file avoiding the use of special characters and any form of encryption. Comment and data will also be accepted on disks in Wordperfect 5.1/6.1 file format or ASCII file format. All comments and data in electronic form must be identified by the docket control number (PF–821) and appropriate petition number. Electronic comments on this notice may be filed online at many Federal Depository Libraries.

Authority: 21 U.S.C. 346a.

List of Subjects

Environmental Protection, Administrative practice and procedure, Agricultural commodities, Pesticides and pests, Reporting and recordkeeping requirements.

Dated: August 6, 1998.

Arnold E. Lane,

Acting Director, Registration Division, Office of Pesticide Programs.

Summaries of Petitions

Petitioner summaries of the pesticide petitions are printed below as required by section 408(d)(3) of the FFDCA. The summaries of the petitions were prepared by the petitioner and represent the views of the petitioner. EPA is publishing the petition summaries verbatim without editing them in any way. The petition summary announces the availability of a description of the analytical methods available to EPA for the detection and measurement of the pesticide chemical residues or an explanation of why no such method is needed.

1. PP 7F4815

EPA has received a pesticide petition (PP 7F4815) from Rohm and Haas Company, 100 Independence Mall West, Philadelphia, PA 19106–2399, proposing pursuant to section 408(d) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. 346a(d), to amend 40 CFR Part 180 by establishing a tolerance for residues of tebufenozide [benzoic acid, 3,5-dimethyl-,1–(1,1-dimethylethyl)-2–(4-ethylbenzoyl) hydrazide] in or on the raw agricultural commodity the crop group pome fruit at 1.0 parts per million (ppm) and in or on apple pomace at 3.0 ppm; fat of cattle, goats, sheep and hogs at 0.25 ppm; liver of cattle, goats, sheep and hogs at 0.075 ppm; meat and meatby-products of cattle, goats, sheep and hogs at 0.05 ppm and milk at 0.05 ppm. EPA has determined that the petition contains data or information regarding the elements set forth in section 408(d)(2) of the FFDCA; however, EPA has not fully evaluated the sufficiency of the submitted data at this time or whether the data supports granting of the petition. Additional data may be needed before EPA rules on the petition.

A. Residue Chemistry

1. *Plant metabolism*. The metabolism of tebufenozide in plants (grapes, apples, rice and sugar beets) is adequately understood for the purposes of these tolerances. The metabolism of tebufenozide in all crops was similar and involves oxidation of the alkyl substituents of the aromatic rings primarily at the benzylic positions. The extent of metabolism and degree of

oxidation are a function of time from application to harvest. In all crops, parent compound comprised the majority of the total dosage. None of the metabolites were in excess of 10% of the total dosage.

2. *Analytical method*. High performance liquid chromatographic (HPLC) analytical methods using ultraviolet (UV) or mass selective detection have been validated for pome fruit, processed apple fractions and animal commodities (meat, organ meats, fat and milk). For all matrices, the methods involve extraction by blending with solvents, purification of the extracts by liquid-liquid partitions and final purification of the residues using solid phase extraction column chromatography. The limits of quantitation is 0.02 ppm for pome fruit and processed commodities, meat, meat organs and fat and 0.01 ppm for milk.

B. Toxicological Profile

1. *Acute toxicity*. Tebufenozide has low acute toxicity. Tebufenozide Technical was practically non-toxic by ingestion of a single oral dose in rats and mice (LD_{50} > 5,000 mg/kg) and was practically non-toxic by dermal application (LD_{50} > 5,000 mg/kg). Tebufenozide Technical was not significantly toxic to rats after a 4–hr inhalation exposure with an LC_{50} value of 4.5 mg/L (highest attainable concentration), is not considered to be a primary eye irritant or a skin irritant and is not a dermal sensitizer. An acute neurotoxicity study in rats did not produce any neurotoxic or neuropathologic effects.

2. *Genotoxicty*. Tebufenozide technical was negative (non-mutagenic) in an Ames assay with and without hepatic enzyme activation and in a reverse mutation assay with *E. coli*. Tebufenozide technical was negative in a hypoxanthine guanine phophoribosyl transferase (HGPRT) gene mutation assay using Chinese hamster ovary (CHO) cells in culture when tested with and without hepatic enzyme activation. In isolated rat hepatocytes, tebufenozide technical did not induce unscheduled DNA synthesis (UDS) or repair when tested up to the maximum soluble concentration in culture medium. Tebufenozide did not produce chromosome effects *in vivo* using rat bone marrow cells or *in vitro* using Chinese hamster ovary cells (CHO). On the basis of the results from this battery of tests concluded that tebufenozide is not mutagenic or genotoxic.

3. *Reproductive and developmental toxicity*. —i. No Observable Effect Levels (NOELs) for developmental and maternal toxicity to tebufenozide were established at 1,000 mg/kg/day (Highest Dose Tested) in both the rat and rabbit. No signs of developmental toxicity were exhibited.

ii. In a 2–generation reproduction study in the rat, the reproductive/developmental toxicity NOEL of 12.1 mg/kg/day was 14–fold higher than the parental (systemic) toxicity NOEL 10 ppm 0.85 mg/kg/day. Equivocal reproductive effects were observed only at the 2,000 ppm dose.

iii. In a second rat reproduction study, the equivocal reproductive effects were not observed at 2,000 ppm (the NOEL equal to 149–195 mg/kg/day) and the NOEL for systemic toxicity was determined to be 25 ppm (1.9–2.3 mg/kg/day).

4. *Subchronic toxicity*. —i. The NOEL in a 90–day rat feeding study was 200 ppm (13 mg/kg/day for males, 16 mg/kg/day for females). The Lowest Observable Effect Level (LOEL) was 2,000 ppm (133 mg/kg/day for males, 155 mg/kg/day for females). Decreased body weights in males and females was observed at the LOEL of 2,000 ppm. As part of this study, the potential for tebufenozide to produce subchronic neurotoxicity was investigated. Tebufenozide did not produce neurotoxic or neuropathologic effects when administered in the diets of rats for 3 months at concentrations up to and including the limit dose of 20,000 ppm (NOEL = 1330 mg/kg/day for males, 1,650 mg/kg/day for females).

ii. In a 90–day feeding study with mice, the NOEL was 20 ppm (3.4 and 4.0 mg/kg/day for males and females, respectively). The LOEL was 200 ppm (35.3 and 44.7 mg/kg/day for males and females, respectively). Decreases in body weight gain were noted in male mice at the LOEL of 200 ppm.

iii. A 90–day dog feeding study gave a NOEL of 50 ppm (2.1 mg/kg/day for males and females). The LOEL was 500 ppm (20.1 and 21.4 mg/kg/day for males and females, respectively). At the LOEL, females exhibited a decrease in rate of weight gain and males presented an increased reticulocyte.

iv. A 10–week study was conducted in the dog to examine the reversibility of the effects on hematological parameters that were observed in other dietary studies with the dog. Tebufenozide was administered for 6 weeks in the diet to 4 male dogs at concentrations of either 0 or 1,500 ppm. After the 6th week, the dogs receiving treated feed were switched to the control diet for 4 weeks. Hematological parameters were measured in both groups prior to treatment, at the end of the 6–week treatment, after 2 weeks of recovery on the control diet and after 4 weeks of recovery on the control diet. All hematological parameters in the treated/recovery group were returned to control levels indicating that the effects of tebufenozide on the hemopoietic system are reversible in the dog.

v. In a 28–day dermal toxicity study in the rat, the NOEL was 1,000 mg/kg/day, the highest dose tested. Tebufenozide did not produce toxicity in the rat when administered dermally for 4 weeks at doses up to and including the limit dose of 1,000 mg/kg/day.

5. *Chronic toxicity*.—i. A 1–year feeding study in dogs resulted in decreased red blood cells, hematocrit, and hemoglobin and increased Heinz bodies, reticulocytes, and platelets at the lowest-observed-effect-level (LOEL) of 8.7 mg/kg/day. The NOEL in this study was 1.8 mg/kg/day.

ii. An 18–month mouse carcinogenicity study showed no signs of carcinogenicity at dosage levels up to and including 1,000 ppm, the highest dose tested.

iii. In a combined rat chronic/oncogenicity study, the NOEL for chronic toxicity was 100 ppm (4.8 and 6.1 mg/kg/day for males and females, respectively) and the LOEL was 1,000 ppm (48 and 61 mg/kg/day for males and females, respectively). No carcinogenicity was observed at the dosage levels up to 2,000 ppm (97 mg/kg/day and 125 mg/kg/day for males and females, respectively).

6. *Animal metabolism*. The adsorption, distribution, excretion and metabolism of tebufenozide in rats was investigated. Tebufenozide is partially absorbed, is rapidly excreted and does not accumulate in tissues. Although tebufenozide is mainly excreted unchanged, a number of polar metabolites were identified. These metabolites are products of oxidation of the benzylic ethyl or methyl side chains of the molecule. These metabolites were detected in plant and other animal (rat, goat, hen) metabolism studies.

7. *Metabolite toxicology*. Common metabolic pathways for tebufenozide have been identified in both plants (grape, apple, rice and sugar beet) and animals (rat, goat, hen). The metabolic pathway common to both plants and animals involves oxidation of the alkyl substituents (ethyl and methyl groups) of the aromatic rings primarily at the benzylic positions. Extensive degradation and elimination of polar metabolites occurs in animals such that residue are unlikely to accumulate in humans or animals exposed to these residues through the diet.

8. *Endocrine disruption*. The toxicology profile of tebufenozide shows no evidence of physiological effects characteristic of the disruption of the

hormone estrogen. Based on structure-activity information, tebufenozide is unlikely to exhibit estrogenic activity. Tebufenozide was not active in a direct *in vitro* estrogen binding assay. No indicators of estrogenic or other endocrine effects were observed in mammalian chronic studies or in mammalian and avian reproduction studies. Ecdysone has no known effects in vertebrates. Overall, the weight of evidence provides no indication that tebufenozide has endocrine activity in vertebrates.

C. Aggregate Exposure

1. *Dietary exposure*. The Reference Dose (RfD) represents the level at or below which daily aggregate dietary exposure over a lifetime will not pose appreciable risks to human health. The RfD is determined by using the toxicological endpoint or the NOEL for the most sensitive mammalian toxicology study. To assure the adequacy of the RfD, the Agency uses an uncertainty factor, usually 100 to account for both interspecies extrapolation and intraspecies variability represented by the toxicological data. The RfD Committee of the USEPA Health Effects Division established the RfD for tebufenozide at 0.018 milligrams (mg)/kilogram (kg)/day based on the 1 year feeding study in dogs. An uncertainty factor of 100 was applied to the NOEL of 1.8 mg/kg/day.

2. *Food*. Tolerances for residues of tebufenozide are currently expressed as benzoic acid, 3,5-dimethyl-1–(1,1-dimethylethyl)-2(4-ethylbenzoyl) hydrazide. Tolerances currently exist for residues on apples at 1.0 ppm (import tolerance) and on walnuts at 0.1 ppm (see 40 CFR 180.482). In addition to this action, a request to establish tolerances for the crop group pome fruit and for livestock commodities, other petitions are pending for the following tolerances: pecans, wine grapes (import tolerance), cotton, the crop subgroups leafy greens, leaf petioles, head and stem Brassica and leafy Brassica greens, and kiwifruit (import tolerance).

i. *Acute risk*. No appropriate acute dietary endpoint was identified by the Agency. This risk assessment is not required.

ii. *Chronic risk*. For chronic dietary risk assessment, the tolerance values are used and the assumption that all of these crops which are consumed in the U.S. will contain residues at the tolerance level. The theoretical maximum residue contribution (TMRC) using existing and future potential tolerances for tebufenozide on food crops is obtained by multiplying the tolerance level residues (existing and proposed) by the consumption data which estimates the amount of those food products consumed by various population subgroups and assuming that 100% of the food crops grown in the U.S. are treated with tebufenozide. The Theoretical Maximum Residue Contribution (TMRC) from current and future tolerances is calculated using the Dietary Exposure Evaluation Model (Version 5.03b, licensed by Novigen Sciences Inc.) which uses USDA food consumption data from the 1989–1992 survey.

With the current and proposed uses of tebufenozide, the TMRC estimate represents 20.1% of the RfD for the U.S. population as a whole. The subgroup with the greatest chronic exposure is non-nursing infants (less than 1 year old), for which the TMRC estimate represents 52.0% of the RfD. Using anticipate residue levels for these crops utilizes 3.38% of the RfD for the U.S. population and 12.0% for non-nursing infants. The chronic dietary risks from these uses do not exceed EPA's level of concern.

3. *Drinking water*. An additional potential source of dietary exposure to residues of pesticides are residues in drinking water. Review of environmental fate data by the Environmental Fate and Effects Division concludes that tebufenozide is moderately persistent to persistent and mobile, and could potentially leach to groundwater and runoff to surface water under certain environmental conditions. However, in terrestrial field dissipation studies, residues of tebufenozide and its soil metabolites showed no downward mobility and remained associated with the upper layers of soil. Foliar interception (up to 60% of the total dosage applied) by target crops reduces the ground level residues of tebufenozide. There is no established Maximum Concentration Level (MCL) for residues of tebufenozide in drinking water. No drinking water health advisory levels have been established for tebufenozide.

There are no available data to perform a quantitative drinking water risk assessment for tebufenozide at this time. However, in order to mitigate the potential for tebufenozide to leach into groundwater or runoff to surface water, precautionary language has been incorporated into the product label. Also, to the best of our knowledge, previous experience with more persistent and mobile pesticides for which there have been available data to perform quantitative risk assessments have demonstrated that drinking water exposure is typically a small percentage of the total exposure when compared to the total dietary exposure. This observation holds even for pesticides detected in wells and drinking water at levels nearing or exceeding established MCLs. Considering the precautionary language on the label and based on our knowledge of previous experience with persistent chemicals, significant exposure from residues of tebufenozide in drinking water is not anticipated.

4. *Non-dietary exposure*. Tebufenozide is not registered for either indoor or outdoor residential use. Non-occupational exposure to the general population is therefore not expected and not considered in aggregate exposure estimates.

D. Cumulative Effects

The potential for cumulative effects of tebufenozide with other substances that have a common mechanism of toxicity was considered. Tebufenozide belongs to the class of insecticide chemicals known as diacylhydrazines. The only other diacylhydrazine currently registered for non-food crop uses is halofenozide. Tebufenozide and halofenozide both produce a mild, reversible anemia following subchronic/chronic exposure at high doses; however, halofenozide also exhibits other patterns of toxicity (liver toxicity following subchronic exposure and developmental/systemic toxicity following acute exposure) which tebufenozide does not. Given the different spectrum of toxicity produced by tebufenozide, there is no reliable data at the molecular/mechanistic level which would indicate that toxic effects produced by tebufenozide would be cumulative with those of halofenozide (or any other chemical compound).

In addition to the observed differences in mammalian toxicity, tebufenozide also exhibits unique toxicity against target insect pests. Tebufenozide is an agonist of 20–hydroxyecdysone, the insect molting hormone, and interferes with the normal molting process in target lepidopteran species by interacting with ecdysone receptors from those species. Unlike other ecdysone agonists such as halofenozide, tebufenozide does not produces symptoms which may be indicative of systemic toxicity in beetle larvae (Coleopteran species). Tebufenozide has a different spectrum of activity than other ecdysone agonists. In contrast to the other agonists such as halofenozide which act mainly on coleopteran insects, tebufenozide is highly specific for lepidopteran insects.

Based on the overall pattern of toxicity produced by tebufenozide in mammalian and insect systems, the compound's toxicity appears to be

distinct from that of other chemicals, including organochlorines, organophosphates, carbamates, pyrethroids, benzoylureas, and other diacylhydrazines. Thus, there is no evidence to date to suggest that cumulative effects of tebufenozide and other chemicals should be considered.

E. Safety Determination

1. *U.S. population*.Using the conservative exposure assumptions described above and taking into account the completeness and reliability of the toxicity data, the dietary exposure to tebufenozide from the current and future tolerances will utilize 20.1% of the RfD for the U.S. population and 52.0% for non-nursing infants under 1 year old. Using anticipate residue levels for these crops utilizes 3.38% of the RfD for the U.S. population and 12.0% for non-nursing infants. EPA generally has no concern for exposures below 100% of the RfD because the RfD represents the level at or below which daily aggregate dietary exposure over a lifetime will not pose appreciable risks to human health. Rohm and Haas concludes that there is a reasonable certainty that no harm will result from aggregate exposure to tebufenozide residues to the U.S. population and non-nursing infants.

2. *Infants and children*. In assessing the potential for additional sensitivity of infants and children to residues of tebufenozide, data from developmental toxicity studies in the rat and rabbit and two 2–generation reproduction studies in the rat are considered. The developmental toxicity studies are designed to evaluate adverse effects on the developing organism resulting from pesticide exposure during prenatal development to one or both parents. Reproduction studies provide information relating to effects from exposure to the pesticide on the reproductive capability of mating animals and data on systemic toxicity. Developmental toxicity was not observed in developmental studies using rats and rabbits. The NOEL for developmental effects in both rats and rabbits was 1,000 mg/kg/day, which is the limit dose for testing in developmental studies.

In the 2–generation reproductive toxicity study in the rat, the reproductive/ developmental toxicity NOEL of 12.1 mg/kg/day was 14–fold higher than the parental (systemic) toxicity NOEL (0.85 mg/kg/day). The reproductive (pup) LOEL of 171.1 mg/kg/day was based on a slight increase in both generations in the number of pregnant females that either did not deliver or had difficulty and had to be sacrificed. In addition, the length of gestation increased and implantation sites decreased significantly in F1 dams. These effects were not replicated at the same dose in a second 2–generation rat reproduction study. In this second study, reproductive effects were not observed at 2,000 ppm (the NOEL equal to 149–195 mg/kg/day) and the NOEL for systemic toxicity was determined to be 25 ppm (1.9–2.3 mg/kg/day).

Because these reproductive effects occurred in the presence of parental (systemic) toxicity and were not replicated at the same doses in a second study, these data do not indicate an increased pre-natal or post-natal sensitivity to children and infants (that infants and children might be more sensitive than adults) to tebufenozide exposure. FFDCA section 408 provides that EPA shall apply an additional safety factor for infants and children in the case of threshold effects to account for pre- and post-natal toxicity and the completeness of the data base unless EPA concludes that a different margin of safety is appropriate. Based on current toxicological data discussed above, an additional uncertainty factor is not warranted and the RfD at 0.018 mg/kg/day is appropriate for assessing aggregate risk to infants and children. Rohm and Haas concludes that there is a reasonable certainty that no harm will occur to infants and children from aggregate exposure to residues of tebufenozide.

F. International Tolerances

There are no approved CODEX maximum residue levels (MRLs) established for residues of tebufenozide. At the 1996 Joint Meeting for Pesticide Residues, the FAO expert panel considered residue data for pome fruit and proposed an MRL (Step 3) of 1.0 mg/kg.

2. PP 7F4819

EPA has received a pesticide petition (PP 7F4819) from Rohm and Haas Company, 100 Independence Mall West, Philadelphia, PA. 19106–2399, proposing pursuant to section 408(d) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. 346a(d), to amend 40 CFR Part 180 by establishing a tolerance for residues of tebufenozide [benzoic acid, 3,5-dimethyl-, 1–(1,1-dimethylethyl)-2–(4-ethylbenzoyl hydrazide] in or on the raw agricultural commodity cottonseed and cotton gin trash at 1.5 and 30 parts per million (ppm) repectively. EPA has determined that the petition contains data or information regarding the elements set forth in section 408(d)(2) of the FFDCA; however, EPA has not fully evaluated the sufficiency of the submitted data at this time or whether the data supports granting of the petition. Additional data may be needed before EPA rules on the petition.

A. Residue Chemistry

1. *Plant metabolism*. The metabolism of tebufenozide in plants (grapes, apples, rice and sugar beets) is adequately understood for the purpose of these tolerances. The metabolism of tebufenozide in all crops was similar and involves oxidation of the alkyl substituents of the aromatic rings primarily at the benzylic positions. The extent of metabolism and degree of oxidation are a function of time from application to harvest. In all crops, parent compound comprised the majority of the total dosage. None of the metabolites were in excess of 10% of the total dosage. The metabolism of tebufenozide in goats and hens proceeds along the same metabolic pathway as observed in plants. No accumulation of residues in tissues, milk or eggs occurred. The metabolic pathway in rotation crops follows the same scheme as in other soil, plant and animal studies although a greater proportion of conjugated metabolites rather than parent were identified in these crops.

2. *Analytical method*. High performance liquid chromatographic (HPLC) analytical methods using ultraviolet (UV) or mass selective detection have been validated for cottonseed, gin trash and cottonseed processed fractions. For all matrices, the methods involve extraction by blending with solvents, purification of the extracts by liquid-liquid partitions and final purification of the residues using solid phase extraction column chromatography. The limits of quantitation are 0.01 ppm for cottonseed, meal and hulls and 0.025 ppm for refined oil and gin trash.

3. *Magnitude of residues*. A total of 15 cotton residue trials were conducted in the U.S. in geographically diverse regions. Four applications of CONFIRM were made at 0.25 lb. a.i./A. Cotton was harvested 13 to 14 days after the last application. Tebufenozide residues in cottonseed ranged from 0.0405 to 1.43 ppm. The average residue from all GAP trials is 0.448. Residues of tebufenozide in gin trash ranged from 1.23 to 30.1 ppm. Residues did not concentrate in cottonseed processed fractions (hulls, meal or refined oil).

B. Toxicological Profile

1. *Acute toxicity*. Tebufenozide has low acute toxicity. Tebufenozide Technical was practically non-toxic by ingestion of a single oral dose in rats and mice (LD_{50} > 5,000 milligram/

kilogram (mg/kg)) and was practically non-toxic by dermal application (LD_{50} > 5,000 mg/kg). Tebufenozide Technical was not significantly toxic to rats after a 4–hr inhalation exposure with an LC_{50} value of 4.5 mg/L (highest attainable concentration), is not considered to be a primary eye irritant or a skin irritant and is not a dermal sensitizer. An acute neurotoxicity study in rats did not produce any neurotoxic or neuropathologic effects.

2. *Genotoxicty*. Tebufenozide technical was negative (non-mutagenic) in an Ames assay with and without hepatic enzyme activation and in a reverse mutation assay with *E. coli*. Tebufenozide technical was negative in a hypoxanthine guanine phophoribosyl transferase (HGPRT) gene mutation assay using Chinese hamster ovary (CHO) cells in culture when tested with and without hepatic enzyme activation. In isolated rat hepatocytes, tebufenozide technical did not induce unscheduled DNA synthesis (UDS) or repair when tested up to the maximum soluble concentration in culture medium. Tebufenozide did not produce chromosome effects *in vivo* using rat bone marrow cells or *in vitro* using Chinese hamster ovary cells (CHO). On the basis of the results from this battery of tests, it is concluded that tebufenozide is not mutagenic or genotoxic.

3. *Reproductive and developmental toxicity*. —i. No Observable Effect Levels (NOELs) for developmental and maternal toxicity to tebufenozide were established at 1,000 milligrams/kilogram/day (mg/kg/day) highest dose tested (HDT) in both the rat and rabbit. No signs of developmental toxicity were exhibited.

ii. In a 2–generation reproduction study in the rat, the reproductive/developmental toxicity NOEL of 12.1 mg/kg/day was 14–fold higher than the parental (systemic) toxicity NOEL 10 ppm (0.85 mg/kg/day). Equivocal reproductive effects were observed only at the 2,000 ppm dose.

iii. In a second rat reproduction study, the equivocal reproductive effects were not observed at 2,000 ppm (the NOEL, equal to 149–195 mg/kg/day) and the NOEL for systemic toxicity was determined to be 25 ppm (1.9–2.3 mg/kg/day).

4. *Subchronic toxicity*. —i. The NOEL in a 90–day rat feeding study was 200 ppm (13 mg/kg/day for males, 16 mg/kg/day for females). The lowest-observed-effect-level (LOEL) was 2,000 ppm (133 mg/kg/day for males, 155 mg/kg/day for females). Decreased body weights in males and females was observed at the LOEL of 2,000 ppm. As part of this study, the potential for tebufenozide to produce subchronic neurotoxicity was investigated. Tebufenozide did not produce neurotoxic or neuropathologic effects when administered in the diets of rats for 3 months at concentrations up to and including the limit dose of 20,000 ppm (NOEL = 1,330 mg/kg/day for males, 1,650 mg/kg/day for females).

ii. In a 90–day feeding study with mice, the NOEL was 20 ppm (3.4 and 4.0 mg/kg/day for males and females, respectively). The LOEL was 200 ppm (35.3 and 44.7 mg/kg/day for males and females, respectively). Decreases in body weight gain were noted in male mice at the LOEL of 200 ppm.

iii. A 90–day dog feeding study gave a NOEL of 50 ppm (2.1 mg/kg/day for males and females). The LOEL was 500 ppm (20.1 and 21.4 mg/kg/day for males and females, respectively). At the LOEL, females exhibited a decrease in rate of weight gain and males presented an increased reticulocyte.

iv. A 10–week study was conducted in the dog to examine the reversibility of the effects on hematological parameters that were observed in other dietary studies with the dog. Tebufenozide was administered for 6 weeks in the diet to 4 male dogs at concentrations of either 0 or 1,500 ppm. After the 6th week, the dogs receiving treated feed were switched to the control diet for 4 weeks. Hematological parameters were measured in both groups prior to treatment, at the end of the 6–week treatment, after 2 weeks of recovery on the control diet and after 4 weeks of recovery on the control diet. All hematological parameters in the treated/recovery group were returned to control levels indicating that the effects of tebufenozide on the hemopoietic system are reversible in the dog.

v. In a 28–day dermal toxicity study in the rat, the NOEL was 1,000 mg/kg/day (HDT). Tebufenozide did not produce toxicity in the rat when administered dermally for 4 weeks at doses up to and including the limit dose of 1,000 mg/kg/day.

5. *Chronic toxicity*. —i. A 1–year feeding study in dogs resulted in decreased red blood cells, hematocrit, and hemoglobin and increased Heinz bodies, reticulocytes, and platelets at the LOEL of 8.7 mg/kg/day. The NOEL in this study was 1.8 mg/kg/day.

ii. An 18–month mouse carcinogenicity study showed no signs of carcinogenicity at dosage levels up to and including 1,000 ppm, the highest dose tested.

iii. In a combined rat chronic/oncogenicity study, the NOEL for chronic toxicity was 100 ppm (4.8 and 6.1 mg/kg/day for males and females, respectively) and the LOEL was 1,000 ppm (48 and 61 mg/kg/day for males and females, respectively). No carcinogenicity was observed at the dosage levels up to 2,000 ppm (97 mg/kg/day and 125 mg/kg/day for males and females, respectively).

6. *Animal metabolism*. The adsorption, distribution, excretion and metabolism of tebufenozide in rats was investigated. Tebufenozide is partially absorbed, is rapidly excreted and does not accumulate in tissues. Although tebufenozide is mainly excreted unchanged, a number of polar metabolites were identified. These metabolites are products of oxidation of the benzylic ethyl or methyl side chains of the molecule. These metabolites were detected in plant and other animal (rat, goat, hen) metabolism studies.

7. *Metabolite toxicology*. Common metabolic pathways for tebufenozide have been identified in both plants (grape, apple, rice and sugar beet) and animals (rat, goat, hen). Extensive degradation and elimination of polar metabolites occurs in animals such that residues are unlikely to accumulate in humans or animals exposed to these residues through the diet.

8. *Endocrine disruption*. The toxicology profile of tebufenozide shows no evidence of physiological effects characteristic of the disruption of the hormone estrogen. Based on structure-activity information, tebufenozide is unlikely to exhibit estrogenic activity. Tebufenozide was not active in a direct *in vitro* estrogen binding assay. No indicators of estrogenic or other endocrine effects were observed in mammalian chronic studies or in mammalian and avian reproduction studies. Ecdysone has no known effects in vertebrates. Overall, the weight of evidence provides no indication that tebufenozide has endocrine activity in vertebrates.

C. Aggregate Exposure

1. *Dietary exposure*. Tolerances have been established (40 CFR 180.482) for the residues of tebufenozide, in or on walnuts at 0.1 ppm. A permanent tolerance at 1.0 ppm has also previously been established for imported apples. Risk assessments were conducted by Rohm and Haas to assess dietary exposures and risks from tebufenozide as follows:

2. *Food*. — i. *Acute exposure and risk*. No acute endpoint was identified for tebufenozide and no acute risk assessment is required.

ii. *Chronic exposure and risk*. For chronic dietary risk assessment, only permanent (walnuts and imported apples) and the proposed (cottonseed,

gin trash) tolerance values are used and the assumption that 100% of all walnuts, imported apples and cottonseed meal and oil which are consumed in the U.S. will contain residues of tebufenozide at the tolerance levels. The Reference Dose (RfD) used for the chronic dietary analysis is 0.018 mg/kg/day. Potential chronic exposures were estimated using NOVIGEN'S Dietary Exposure Evaluation Model (DDEM Version 5.03b) which uses USDA food consumption data from the 1989–1992 survey. With the current and proposed tolerances for tebufenozide, the percentage of the RfD utilized is 6.95% for the U.S. population as a whole and 46.2% for non-nursing infants less than 1 year old. The chronic dietary risks from these uses do not exceed EPA's level of concern.

3. *Drinking water.* Submitted environmental fate studies suggest that tebufenozide is moderately persistent to persistent and mobile, and could potentially leach to groundwater and runoff to surface water under certain environmental conditions. However, in terrestrial field dissipation studies, residues of tebufenozide and its soil metabolites showed no downward mobility and remained associated with the upper layers of soil. Foliar interception (up to 60% of the total dosage applied) by target crops reduces the ground level residues of tebufenozide. There is no established Maximum Concentration Level (MCL) for residues of tebufenozide in drinking water. No drinking water health advisory levels have been established for tebufenozide. There is no entry for tebufenozide in the ''Pesticides in Groundwater Database'' (EPA 734–12–92–001, September 1992).

Chronic exposure and risk. There are insufficient water-related exposure data to complete a comprehensive drinking water assessment for tebufenozide at this time. However, in order to mitigate the potential for tebufenozide to leach into groundwater or runoff to surface water, precautionary language has been incorporated into the product label. Also, to the best of our knowledge, previous experience with more persistent and mobile pesticides for which there have been available data to perform quantitative risk assessments have demonstrated that drinking water exposure is typically a small percentage of the total exposure when compared to the total dietary exposure. This observation holds even for pesticides detected in wells and drinking water at levels nearing or exceeding established MCLs. Considering the precautionary language on the label and based on our knowledge of previous experience with persistent chemicals, significant exposure from residues of tebufenozide in drinking water is not anticipated.

4. *Non-dietary exposure.* Tebufenozide is not currently registered for any indoor or outdoor residential uses; therefore, no non-dietary residential exposure is anticipated.

D. Cumulative Effects

The potential for cumulative effects of tebufenozide with other substances that have a common mechanism of toxicity was considered. Tebufenozide belongs to the class of insecticide chemicals known as diacylhydrazines. The only other diacylhydrazine currently registered for non-food crop uses is halofenozide. Tebufenozide and halofenozide both produce a mild, reversible anemia following subchronic/chronic exposure at high doses; however, halofenozide also exhibits other patterns of toxicity (liver toxicity following subchronic exposure and developmental/systemic toxicity following acute exposure) which tebufenozide does not. Given the different spectrum of toxicity produced by tebufenozide, there is no reliable data at the molecular/mechanistic level which would indicate that toxic effects produced by tebufenozide would be cumulative with those of halofenozide (or any other chemical compound).

In addition to the observed differences in mammalian toxicity, tebufenozide also exhibits unique toxicity against target insect pests. Tebufenozide is an agonist of 20–hydroxyecdysone, the insect molting hormone, and interferes with the normal molting process in target lepidopteran species by interacting with ecdysone receptors from those species. Unlike other ecdysone agonists such as halofenozide, tebufenozide does not produces symptoms which may be indicative of systemic toxicity in beetle larvae (Coleopteran species). Tebufenozide has a different spectrum of activity than other ecdysone agonists. In contrast to the other agonists such as halofenozide which act mainly on coleopteran insects, tebufenozide is highly specific for lepidopteran insects.

Based on the overall pattern of toxicity produced by tebufenozide in mammalian and insect systems, the compound's toxicity appears to be distinct from that of other chemicals, including organochlorines, organophosphates, carbamates, pyrethroids, benzoylureas, and other diacylhydrazines. Thus, there is no evidence to date to suggest that cumulative effects of tebufenozide and other chemicals should be considered.

E. Safety Determination

1. *U.S. population.* —i. *Acute exposure and risk.* Since no acute endpoint was identified for tebufenozide, no acute risk assessment is required.

ii. *Chronic exposure and risk.* Using the conservative exposure assumptions described above and taking into account the completeness and reliability of the toxicity data, the percentage of the RfD that will be utilized by dietary (food only) exposure to residues of tebufenozide from current (walnuts and imported apples) and proposed (cottonseed, gin trash) tolerances is 6.95% for the U.S. population. Aggregate exposure (food and water) are not expected to exceed 100%. EPA generally has no concern for exposures below 100% of the RfD because the RfD represents the level at or below which daily aggregate dietary exposure over a lifetime will not pose appreciable risks to human health. Rohm and Haas concludes that there is a reasonable certainty that no harm will result from aggregate exposure to tebufenozide residues to the U.S. population.

2. *Infants and children.* —i. *Safety factor for infants and children...In general.* In assessing the potential for additional sensitivity of infants and children to residues of tebufenozide, data from developmental toxicity studies in the rat and rabbit and 2–generation reproduction studies in the rat are considered. The developmental toxicity studies are designed to evaluate adverse effects on the developing organism resulting from maternal pesticide exposure during gestation. Reproduction studies provide information relating to effects from exposure to the pesticide on the reproductive capability of mating animals and data on systemic toxicity.

ii. *Developmental toxicity studies — a. Rats.* In a developmental toxicity study in rats, the maternal (systemic) NOEL was 250 mg/kg/day. The LOEL was 1,000 mg/kg/day based on decrease body weight and food consumption. The developmental (pup) NOEL as > 1,000 mg/kg/day (HDT).

b. Rabbits. In a developmental toxicity study in rabbits, the maternal and developmental NOELs were > 1,000 mg/kg/day (HDT).

iii. *Reproductive toxicity study Rats.* In a multigeneration reproductive toxicity study in rats, the parental (systemic) NOEL was 0.85 mg/kg/day. Spleenic pigmentation changes and extramedullary hematopoiesis occurred at the LOEL of 12.1 mg/kg/day. In addition to these effects, decreased body weight gain and food consumption

occurred at 171.1 mg/kg/day. The reproductive (pup) NOEL was 12.1 mg/kg/day. The reproductive LOEL of 171.1 mg/kg/day was based on a slight increase in the number of pregnant females that did not deliver or had difficulty and had to be sacrificed. Additionally at the LOEL, in F1 dams, the length of gestation increased and implantation sites decreased significantly. In a second study, reproductive effects were not observed at 2,000 ppm (the NOEL equal to 149–195 mg/kg/day) and the NOEL for systemic toxicity was determined to be 25 ppm (1.9–2.3 mg/kg/day).

iv. *Pre- and post-natal sensitivity — a. Pre-natal sensitivity.* The developmental NOELs of >1,000 mg/kg/day (HDT) from the developmental toxicity studies in rats and rabbits demonstrate that there is no developmental (prenatal) toxicity present for tebufenozide. Additionally, these developmental NOELs are greater than 500–fold higher than the NOEL of 1.8 mg/kg/day from the 1–year feeding study in dogs which was the basis of the RfD.

b. Post-natal sensitivity. In the reproductive toxicity study in rats, the reproductive NOEL (12.1 mg/kg/day from the first study; 149–195 mg/kg/day from the second study) is between 14–fold higher than the parental NOEL (0.85 mg/kg/day) in the first study and 83–fold higher than the parental NOEL (1.8–2.3 mg/kg/day) in the second study. These data indicate that post-natal toxicity in the reproductive studies occurs only in the presence of significant parental toxicity. These developmental and reproductive studies indicate that tebufenozide does not have additional post-natal sensitivity for infants and children in comparison to other exposed groups. Because these reproductive effects occurred in the presence of parental (systemic) toxicity and were not replicated at the same doses in a second study, these data do not indicate an increased pre-natal or post-natal sensitivity to children and infants (that infants and children might be more sensitive than adults) to tebufenozide exposure.

v. *Acute exposure and risk.* Since no acute endpoint was identified for tebufenozide, no acute risk assessment is required.

vi. *Chronic exposure and risk.* For chronic dietary risk assessment, tolerance values are used and the assumption that all walnuts, imported apples and cottonseed meal and oil which are consumed in the U.S. will contain residues at the tolerance levels. The Theoretical Maximum Residue Contribution (TMRC) from current and proposed food tolerances is calculated using the Dietary Exposure Evaluation Model (Version 5.03b, licensed by Novigen Sciences Inc.) which uses USDA food consumption data from the 1989–1992 survey. With the current (walnuts and imported apples) and proposed (cottonseed, gin trash) tolerances for tebufenozide, the percentage of the RfD that will be utilized by dietary (food only) exposure to residues of tebufenozide is 46.2% for non-nursing infants less than 1 year old. Aggregate exposure (food and water) are not expected to exceed 100%. Rohm and Haas concludes that there is a reasonable certainty that no harm will result from aggregate exposure to tebufenozide residues to non-nursing infants.

F. International Tolerances

There are currently no CODEX or Canadian maximum residue levels (MRLs) established for tebufenozide in cottonseed or gin trash. A Mexican MRL of 0.5 ppm for cottonseed has been established.

3. PP 7F4824

EPA has received a pesticide petition (PP 7F4824) from Rohm and Haas Company, 100 Independence mall West, Philadelphia, PA 19106–2399, proposing pursuant to section 408(d) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. 346a(d), to amend 40 CFR Part 180 by establishing a tolerance for residues of tebufenozide [benzoic acid, 3,5-dimethyl-, 1–(1,1-dimethylethyl)-2–(4-ethylbenzoyl) hydrazide] in or on the raw agricultural commodity leafy greens, leaf petioles, head and stem Brassica, and leafy Brassica greens at 6.0, 2.0, 2.0, and 10 parts per million (ppm) respectively. EPA has determined that the petition contains data or information regarding the elements set forth in section 408(d)(2) of the FFDCA; however, EPA has not fully evaluated the sufficiency of the submitted data at this time or whether the data supports granting of the petition. Additional data may be needed before EPA rules on the petition.

A. Residue Chemistry

1. *Plant and Animal metabolism.* The metabolism of tebufenozide in plants (grapes, apples, rice and sugar beets) is adequately understood for the purposes of these tolerances. The metabolism of tebufenozide in all crops was similar and involves oxidation of the alkyl substituents of the aromatic rings primarily at the benzylic positions. The extent of metabolism and degree of oxidation are a function of time from application to harvest. In all crops, parent compound comprised the majority of the total dosage. None of the metabolites were in excess of 10% of the total dosage. The metabolism of tebufenozide in goats and hens proceeds along the same metabolic pathway as observed in plants. No accumulation of residues in tissues, milk or eggs occurred.

2. *Analytical method.* A high performance liquid chromatographic (HPLC) analytical method using ultraviolet (UV) detection has been validated for leafy and cole crop vegetables. For all matrices, the methods involve extraction by blending with solvents, purification of the extracts by liquid-liquid partitions and final purification of the residues using solid phase extraction column chromatography. The limit of quantitation of the method is 0.01 ppm for all representative crops of these crop subgroups except for celery which is 0.05 ppm.

B. Toxicological Profile

1. *Acute toxicity.* Tebufenozide has low acute toxicity. Tebufenozide Technical was practically non-toxic by ingestion of a single oral dose in rats and mice (LD_{50} > 5,000 mg/kg) and was practically non-toxic by dermal application (LD_{50} > 5,000 mg/kg). Tebufenozide Technical was not significantly toxic to rats after a 4–hr inhalation exposure with an LC_{50} value of 4.5 mg/L (highest attainable concentration), is not considered to be a primary eye irritant or a skin irritant and is not a dermal sensitizer. An acute neurotoxicity study in rats did not produce any neurotoxic or neuropathologic effects.

2. *Genotoxicty.* Tebufenozide technical was negative (non-mutagenic) in an Ames assay with and without hepatic enzyme activation and in a reverse mutation assay with *E. coli.* Tebufenozide technical was negative in a hypoxanthine guanine phophoribosyl transferase (HGPRT) gene mutation assay using Chinese hamster ovary (CHO) cells in culture when tested with and without hepatic enzyme activation. In isolated rat hepatocytes, tebufenozide technical did not induce unscheduled DNA synthesis (UDS) or repair when tested up to the maximum soluble concentration in culture medium. Tebufenozide did not produce chromosome effects *in vivo* using rat bone marrow cells or *in vitro* using Chinese hamster ovary cells (CHO). On the basis of the results from this battery of tests, it is concluded that tebufenozide is not mutagenic or genotoxic.

3. *Reproductive and developmental toxicity.* — i. No Observable Effect

Levels (NOELs) for developmental and maternal toxicity to tebufenozide were established at 1,000 mg/kg/day (Highest Dose Tested) in both the rat and rabbit. No signs of developmental toxicity were exhibited.

ii. In a 2–generation reproduction study in the rat, the reproductive/developmental toxicity NOEL of 12.1 mg/kg/day was 14–fold higher than the parental (systemic) toxicity NOEL 10 ppm 0.85 mg/kg/day. Equivocal reproductive effects wereobserved only at the 2,000 ppm dose.

iii. In a second rat reproduction study, the equivocal reproductive effects were not observed at 2,000 ppm (the NOEL equal to 149–195 mg/kg/day) and the NOEL for systemic toxicity was determined to be 25 ppm (1.9–2.3 mg/kg/day).

4. *Subchronic toxicity.* —i. The NOEL in a 90–day rat feeding study was 200 ppm (13 mg/kg/day for males, 16 mg/kg/day for females). The lowest-observed-effect-level (LOEL) was 2,000 ppm (133 mg/kg/day for males, 155 mg/kg/day for females). Decreased body weights in males and females was observed at the LOEL of 2,000 ppm. As part of this study, the potential for tebufenozide to produce subchronic neurotoxicity was investigated. Tebufenozide did not produce neurotoxic or neuropathologic effects when administered in the diets of rats for 3 months at concentrations up to and including the limit dose of 20,000 ppm (NOEL = 1,330 mg/kg/day for males, 1,650 mg/kg/day for females).

ii. In a 90–day feeding study with mice, the NOEL was 20 ppm (3.4 and 4.0 mg/kg/day for males and females, respectively). The LOEL was 200 ppm (35.3 and 44.7 mg/kg/day for males and females, respectively). Decreases in body weight gain were noted in male mice at the LOEL of 200 ppm.

iii. A 90–day dog feeding study gave a NOEL of 50 ppm (2.1 mg/kg/day for males and females). The LOEL was 500 ppm (20.1 and 21.4 mg/kg/day for males and females, respectively). At the LOEL, females exhibited a decrease in rate of weight gain and males presented an increased reticulocyte.

iv. A 10–week study was conducted in the dog to examine the reversibility of the effects on hematological parameters that were observed in other dietary studies with the dog. Tebufenozide was administered for 6 weeks in the diet to 4 male dogs at concentrations of either 0 or 1,500 ppm. After the 6th week, the dogs receiving treated feed were switched to the control diet for 4 weeks. Hematological parameters were measured in both groups prior to treatment, at the end of the 6–week treatment, after 2 weeks of recovery on the control diet and after 4 weeks of recovery on the control diet. All hematological parameters in the treated/recovery group were returned to control levels indicating that the effects of tebufenozide on the hemopoietic system are reversible in the dog.

v. In a 28–day dermal toxicity study in the rat, the NOEL was 1,000 mg/kg/day, the highest dose tested. Tebufenozide did not produce toxicity in the rat when administered dermally for 4 weeks at doses up to and including the limit dose of 1,000 mg/kg/day.

5. *Chronic toxicity.* —i. A 1 year feeding study in dogs resulted in decreased red blood cells, hematocrit, and hemoglobin and increased Heinz bodies, reticulocytes, and platelets at the Lowest Observed Effect Level (LOEL) of 8.7 mg/kg/day. The NOEL in this study was 1.8 mg/kg/day.

ii. An 18–month mouse carcinogenicity study showed no signs of carcinogenicity at dosage levels up to and including 1,000 ppm, the highest dose tested.

iii. In a combined rat chronic/oncogenicity study, the NOEL for chronic toxicity was 100 ppm (4.8 and 6.1 mg/kg/day for males and females, respectively) and the LOEL was 1,000 ppm (48 and 61 mg/kg/day for males and females, respectively). No carcinogenicity was observed at the dosage levels up to 2,000 ppm (97 mg/kg/day and 125 mg/kg/day for males and females, respectively).

6. *Animal metabolism*. The adsorption, distribution, excretion and metabolism of tebufenozide in rats was investigated. Tebufenozide is partially absorbed, is rapidly excreted and does not accumulate in tissues. Although tebufenozide is mainly excreted unchanged, a number of polar metabolites were identified. These metabolites are products of oxidation of the benzylic ethyl or methyl side chains of the molecule. These metabolites were detected in plant and other animal (rat, goat, hen) metabolism studies.

7. *Metabolite toxicology*. Common metabolic pathways for tebufenozide have been identified in both plants (grape, apple, rice and sugar beet) and animals (rat, goat, hen). The metabolic pathway common to both plants and animals involves oxidation of the alkyl substituents (ethyl and methyl groups) of the aromatic rings primarily at the benzylic positions. Extensive degradation and elimination of polar metabolites occurs in animals such that residue are unlikely to accumulate in humans or animals exposed to these residues through the diet.

8. *Endocrine disruption*. The toxicology profile of tebufenozide shows no evidence of physiological effects characteristic of the disruption of the hormone estrogen. Based on structure-activity information, tebufenozide is unlikely to exhibit estrogenic activity. Tebufenozide was not active in a direct *in vitro* estrogen binding assay. No indicators of estrogenic or other endocrine effects were observed in mammalian chronic studies or in mammalian and avian reproduction studies. Ecdysone has no known effects in vertebrates. Overall, the weight of evidence provides no indication that tebufenozide has endocrine activity in vertebrates.

C. Aggregate Exposure

1. *Dietary exposure*. Use of an agricultural pesticide may result, directly or indirectly in pesticide residues in food. These residues are determined by chemical analysis. Data from field studies are evaluated to determine the appropriate level of residue that would not be exceeded if the pesticide were used according to the label use directions.

In examining aggregate exposure, FQPA directs EPA to consider available information concerning exposures from the pesticide residue in food and all other non-occupational exposures. The primary non-food sources of exposure the Agency looks at include drinking water (whether from groundwater or surface water), and exposure through pesticide use in gardens, lawns or buildings (residential and other indoor uses). In evaluating food exposures, EPA takes into account varying consumption patterns of major identifiable subgroups of consumers, including infants and children.

2. *Food*. Tolerances for residues of tebufenozide are currently expressed as benzoic acid, 3,5-dimethyl-1–(1,1-dimethylethyl)-2(4-ethylbenzoyl) hydrazide. Tolerances currently exist for residues on apples at 1.0 ppm (import tolerance) and on walnuts at 0.1 ppm (see 40 CFR 180.482). In addition to this action, a request to establish tolerances for the crop subgroups leafy greens, leaf petioles, head and stem Brassica and leafy Brassica greens, other petitions are pending for the following tolerances: pome fruit, livestock commodities, pecans, wine grapes (import tolerance), cotton, and kiwifruit (import tolerance).

i. *Acute risk*. No appropriate acute dietary endpoint was identified by the Agency. This risk assessment is not required.

ii. *Chronic risk*. For chronic dietary risk assessment, the tolerance values are used and the assumption that all of these crops which are consumed in the U.S. will contain residues at the

tolerance level. The theoretical maximum residue contribution (TMRC) using existing and future potential tolerances for tebufenozide on food crops is obtained by multiplying the tolerance level residues (existing and proposed) by the consumption data which estimates the amount of those food products consumed by various population subgroups and assuming that 100% of the food crops grown in the U.S. are treated with tebufenozide. The Theoretical Maximum Residue Contribution (TMRC) from current and future tolerances is calculated using the Dietary Exposure Evaluation Model (Version 5.03b, licensed by Novigen Sciences Inc.) which uses USDA food consumption data from the 1989–1992 survey.

With the current and proposed uses of tebufenozide, the TMRC estimate represents 20.1% of the Reference Dose (RfD) for the U.S. population as a whole. The subgroup with the greatest chronic exposure is non-nursing infants (less than 1 year old), for which the TMRC estimate represents 52.0% of the RfD. Using anticipate residue levels for these crops utilizes 3.38% of the RfD for the U.S. population and 12.0% for non-nursing infants. The chronic dietary risks from these uses do not exceed EPA's level of concern.

3. *Drinking water*. An additional potential source of dietary exposure to residues of pesticides are residues in drinking water. Review of environmental fate data by the Environmental Fate and Effects Division concludes that tebufenozide is moderately persistent to persistent and mobile, and could potentially leach to groundwater and runoff to surface water under certain environmental conditions. However, in terrestrial field dissipation studies, residues of tebufenozide and its soil metabolites showed no downward mobility and remained associated with the upper layers of soil. Foliar interception (up to 60% of the total dosage applied) by target crops reduces the ground level residues of tebufenozide. There is no established Maximum Concentration Level (MCL) for residues of tebufenozide in drinking water. No drinking water health advisory levels have been established for tebufenozide.

There are no available data to perform a quantitative drinking water risk assessment for tebufenozide at this time. However, in order to mitigate the potential for tebufenozide to leach into groundwater or runoff to surface water, precautionary language has been incorporated into the product label. Also, to the best of our knowledge, previous experience with more persistent and mobile pesticides for which there have been available data to perform quantitative risk assessments have demonstrated that drinking water exposure is typically a small percentage of the total exposure when compared to the total dietary exposure. This observation holds even for pesticides detected in wells and drinking water at levels nearing or exceeding established MCLs. Considering the precautionary language on the label and based on our knowledge of previous experience with persistent chemicals, significant exposure from residues of tebufenozide in drinking water is not anticipated.

4. *Non-dietary exposure*. Tebufenozide is not registered for either indoor or outdoor residential use. Non-occupational exposure to the general population is therefore not expected and not considered in aggregate exposure estimates.

D. Cumulative Effects

The potential for cumulative effects of tebufenozide with other substances that have a common mechanism of toxicity was considered. Tebufenozide belongs to the class of insecticide chemicals known as diacylhydrazines. The only other diacylhydrazine currently registered for non-food crop uses is halofenozide. Tebufenozide and halofenozide both produce a mild, reversible anemia following subchronic/chronic exposure at high doses; however, halofenozide also exhibits other patterns of toxicity (liver toxicity following subchronic exposure and developmental/systemic toxicity following acute exposure) which tebufenozide does not. Given the different spectrum of toxicity produced by tebufenozide, there is no reliable data at the molecular/mechanistic level which would indicate that toxic effects produced by tebufenozide would be cumulative with those of halofenozide (or any other chemical compound).

In addition to the observed differences in mammalian toxicity, tebufenozide also exhibits unique toxicity against target insect pests. Tebufenozide is an agonist of 20–hydroxyecdysone, the insect molting hormone, and interferes with the normal molting process in target lepidopteran species by interacting with ecdysone receptors from those species. Unlike other ecdysone agonists such as halofenozide, tebufenozide does not produces symptoms which may be indicative of systemic toxicity in beetle larvae (Coleopteran species). Tebufenozide has a different spectrum of activity than other ecdysone agonists. In contrast to the other agonists such as halofenozide which act mainly on coleopteran insects, tebufenozide is highly specific for lepidopteran insects.

Based on the overall pattern of toxicity produced by tebufenozide in mammalian and insect systems, the compound's toxicity appears to be distinct from that of other chemicals, including organochlorines, organophosphates, carbamates, pyrethroids, benzoylureas, and other diacylhydrazines. Thus, there is no evidence to date to suggest that cumulative effects of tebufenozide and other chemicals should be considered.

E. Safety Determination

1. *U.S. population*. Using the conservative exposure assumptions described above and taking into account the completeness and reliability of the toxicity data, the dietary exposure to tebufenozide from the current and future tolerances will utilize 20.1% of the RfD for the U.S. population and 52.0% for non-nursing infants under 1 year old. Using anticipate residue levels for these crops utilizes 3.38% of the RfD for the U.S. population and 12.0% for non-nursing infants. EPA generally has no concern for exposures below 100% of the RfD because the RfD represents the level at or below which daily aggregate dietary exposure over a lifetime will not pose appreciable risks to human health. Rohm and Haas concludes that there is a reasonable certainty that no harm will result from aggregate exposure to tebufenozide residues to the U.S. population and non-nursing infants.

2. *Infants and children*. In assessing the potential for additional sensitivity of infants and children to residues of tebufenozide, data from developmental toxicity studies in the rat and rabbit and two 2–generation reproduction studies in the rat are considered. The developmental toxicity studies are designed to evaluate adverse effects on the developing organism resulting from pesticide exposure during prenatal development to one or both parents. Reproduction studies provide information relating to effects from exposure to the pesticide on the reproductive capability of mating animals and data on systemic toxicity. Developmental toxicity was not observed in developmental studies using rats and rabbits. The NOEL for developmental effects in both rats and rabbits was 1,000 mg/kg/day, which is the limit dose for testing in developmental studies.In the 2–generation reproductive toxicity study in the rat, the reproductive/developmental toxicity NOEL of 12.1 mg/kg/day was 14–fold higher than the parental (systemic) toxicity NOEL (0.85

mg/kg/day). The reproductive (pup) LOEL of 171.1 mg/kg/day was based on a slight increase in both generations in the number of pregnant females that either did not deliver or had difficulty and had to be sacrificed. In addition, the length of gestation increased and implantation sites decreased significantly in F1 dams. These effects were not replicated at the same dose in a second 2–generation rat reproduction study. In this second study, reproductive effects were not observed at 2,000 ppm (the NOEL equal to 149–195 mg/kg/day) and the NOEL for systemic toxicity was determined to be 25 ppm (1.9–2.3 mg/kg/day).

Because these reproductive effects occurred in the presence of parental (systemic) toxicity and were not replicated at the same doses in a second study, these data do not indicate an increased pre-natal or post-natal sensitivity to children and infants (that infants and children might be more sensitive than adults) to tebufenozide exposure. FFDCA section 408 provides that EPA shall apply an additional safety factor for infants and children in the case of threshold effects to account for pre- and post-natal toxicity and the completeness of the data base unless EPA concludes that a different margin of safety is appropriate. Based on current toxicological data discussed above, an additional uncertainty factor is not warranted and the RfD at 0.018 mg/kg/day is appropriate for assessing aggregate risk to infants and children. Rohm and Haas concludes that there is a reasonable certainty that no harm will occur to infants and children from aggregate exposure to residues of tebufenozide.

F. International Tolerances

There are no approved CODEX maximum residue levels (MRLs) established for residues of tebufenozide.

4. PP 7E4829

EPA has received a pesticide petition (PP 7E4829) from Rohm and Haas Company, 100 Independence Mall West, Philadelphia, PA 19106–2399, proposing pursuant to section 408(d) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. 346a(d), to amend 40 CFR Part 180 by establishing a tolerance for residues of tebufenozide [benzoic acid, 3,5-dimethyl-, 1–(1,1-dimethylethyl)-2–(4-ethylbenzoyl) hydrazide in or on the raw agricultural commodity kiwifruit at 0.5 parts per million (ppm). EPA has determined that the petition contains data or information regarding the elements set forth in section 408(d)(2) of the FFDCA; however, EPA has not fully evaluated the sufficiency of the submitted data at this time or whether the data supports granting of the petition. Additional data may be needed before EPA rules on the petition.

A. Residue Chemistry

1. *Plant metabolism*. The metabolism of tebufenozide in plants (grapes, apples, rice and sugar beets) is adequately understood for the purposes of these tolerances. The metabolism of tebufenozide in all crops was similar and involves oxidation of the alkyl substituents of the aromatic rings primarily at the benzylic positions. The extent of metabolism and degree of oxidation are a function of time from application to harvest. In all crops, parent compound comprised the majority of the total dosage. None of the metabolites were in excess of 10% of the total dosage. The metabolism of tebufenozide in goats and hens proceeds along the same metabolic pathway as observed in plants. No accumulation of residues in tissues, milk or eggs occurred.

2. *Analytical method*. A validated high performance liquid chromatographic (HPLC) analytical method using ultraviolet (UV) or mass selective detection is employed for measuring residues of tebufenozide in kiwifruit. The method involves extraction by blending with solvents, purification of the extracts by liquid-liquid partitions and final purification of the residues using solid phase extraction column chromatography. The limit of quantitation of the method is 0.02 ppm.

B. Toxicological Profile

1. *Acute toxicity*. Tebufenozide has low acute toxicity. Tebufenozide Technical was practically non-toxic by ingestion of a single oral dose in rats and mice (LD_{50} > 5,000 mg/kg) and was practically non-toxic by dermal application (LD_{50} > 5,000 mg/kg). Tebufenozide Technical was not significantly toxic to rats after a 4–hr inhalation exposure with an LC_{50} value of 4.5 mg/L (highest attainable concentration), is not considered to be a primary eye irritant or a skin irritant and is not a dermal sensitizer. An acute neurotoxicity study in rats did not produce any neurotoxic or neuropathologic effects.

2. *Genotoxicty*. Tebufenozide technical was negative (non-mutagenic) in an Ames assay with and without hepatic enzyme activation and in a reverse mutation assay with *E. coli*. Tebufenozide technical was negative in a hypoxanthine guanine phophoribosyl transferase (HGPRT) gene mutation assay using Chinese hamster ovary (CHO) cells in culture when tested with and without hepatic enzyme activation. In isolated rat hepatocytes, tebufenozide technical did not induce unscheduled DNA synthesis (UDS) or repair when tested up to the maximum soluble concentration in culture medium. Tebufenozide did not produce chromosome effects *in vivo* using rat bone marrow cells or *in vitro* using Chinese hamster ovary cells (CHO). On the basis of the results from this battery of tests, it is concluded that tebufenozide is not mutagenic or genotoxic.

3. *Reproductive and developmental toxicity*. —i. No Observable Effect Levels (NOELs) for developmental and maternal toxicity to tebufenozide were established at 1,000 mg/kg/day (Highest Dose Tested) in both the rat and rabbit. No signs of developmental toxicity were exhibited.

ii. In a 2–generation reproduction study in the rat, the reproductive/developmental toxicity NOEL of 12.1 mg/kg/day was 14–fold higher than the parental (systemic) toxicity NOEL 10 ppm 0.85 mg/kg/day. Equivocal reproductive effects were observed only at the 2,000 ppm dose.

iii. In a second rat reproduction study, the equivocal reproductive effects were not observed at 2,000 ppm (the NOEL equal to 149–195 mg/kg/day) and the NOEL for systemic toxicity was determined to be 25 ppm (1.9–2.3 mg/kg/day).

4. *Subchronic toxicity*. —i. The NOEL in a 90–day rat feeding study was 200 ppm (13 mg/kg/day for males, 16 mg/kg/day for females). The lowest-observed-effect-level (LOEL) was 2,000 ppm (133 mg/kg/day for males, 155 mg/kg/day for females). Decreased body weights in males and females was observed at the LOEL of 2,000 ppm. As part of this study, the potential for tebufenozide to produce subchronic neurotoxicity was investigated. Tebufenozide did not produce neurotoxic or neuropathologic effects when administered in the diets of rats for 3 months at concentrations up to and including the limit dose of 20,000 ppm (NOEL = 1,330 mg/kg/day for males, 1,650 mg/kg/day for females).

ii. In a 90–day feeding study with mice, the NOEL was 20 ppm (3.4 and 4.0 mg/kg/day for males and females, respectively). The LOEL was 200 ppm (35.3 and 44.7 mg/kg/day for males and females, respectively). Decreases in body weight gain were noted in male mice at the LOEL of 200 ppm.

iii. A 90–day dog feeding study gave a NOEL of 50 ppm (2.1 mg/kg/day for males and females). TheLOEL was 500 ppm (20.1 and 21.4 mg/kg/day for males and females, respectively). At the

LOEL,females exhibited a decrease in rate of weight gain and males presented an increased reticulocyte.

iv. A 10–week study was conducted in the dog to examine the reversibility of the effects on hematological parameters that were observed in other dietary studies with the dog. Tebufenozide was administered for 6 weeks in the diet to 4 male dogs at concentrations of either 0 or 1,500 ppm. After the 6th week, the dogs receiving treated feed were switched to the control diet for 4 weeks. Hematological parameters were measured in both groups prior to treatment, at the end of the 6-week treatment, after 2 weeks of recovery on the control diet and after 4 weeks of recovery on the control diet. All hematological parameters in the treated/recovery group were returned to control levels indicating that the effects of tebufenozide on the hemopoietic system are reversible in the dog.

v. In a 28–day dermal toxicity study in the rat, the NOEL was 1,000 mg/kg/day, the highest dose tested. Tebufenozide did not produce toxicity in the rat when administered dermally for 4 weeks at doses up to and including the limit dose of 1,000 mg/kg/day.

5. *Chronic toxicity*. Chronic Feeding Toxicity and Carcinogenicity:

i. A 1 year feeding study in dogs resulted in decreased red blood cells, hematocrit, and hemoglobin and increased Heinz bodies, reticulocytes, and platelets at the Lowest Observed Effect Level (LOEL) of 8.7 mg/kg/day. The NOEL in this study was 1.8 mg/kg/day.

ii. An 18–month mouse carcinogenicity study showed no signs of carcinogenicity at dosage levels up to and including 1,000 ppm, the highest dose tested.

iii. In a combined rat chronic/oncogenicity study, the NOEL for chronic toxicity was 100 ppm (4.8 and 6.1 mg/kg/day for males and females, respectively) and the LOEL was 1,000 ppm (48 and 61 mg/kg/day for males and females, respectively). No carcinogenicity was observed at the dosage levels up to 2,000 ppm (97 mg/kg/day and 125 mg/kg/day for males and females, respectively).

6. *Animal metabolism*. The adsorption, distribution, excretion and metabolism of tebufenozide in rats was investigated. Tebufenozide is partially absorbed, is rapidly excreted and does not accumulate in tissues. Although tebufenozide is mainly excreted unchanged, a number of polar metabolites were identified. These metabolites are products of oxidation of the benzylic ethyl or methyl side chains of the molecule. These metabolites were detected in plant and other animal (rat, goat, hen) metabolism studies.

7. *Metabolite toxicology*. Common metabolic pathways for tebufenozide have been identified in both plants (grape, apple, rice and sugar beet) and animals (rat, goat, hen). The metabolic pathway common to both plants and animals involves oxidation of the alkyl substituents (ethyl and methyl groups) of the aromatic rings primarily at the benzylic positions. Extensive degradation and elimination of polar metabolites occurs in animals such that residue are unlikely to accumulate in humans or animals exposed to these residues through the diet.

8. *Endocrine disruption*. Estrogenic Effects. The toxicology profile of tebufenozide shows no evidence of physiological effects characteristic of the disruption of the hormone estrogen. Based on structure-activity information, tebufenozide is unlikely to exhibit estrogenic activity. Tebufenozide was not active in a direct *in vitro* estrogen binding assay. No indicators of estrogenic or other endocrine effects were observed in mammalian chronic studies or in mammalian and avian reproduction studies. Ecdysone has no known effects in vertebrates. Overall, the weight of evidence provides no indication that tebufenozide has endocrine activity in vertebrates.

C. Aggregate Exposure

1. *Dietary exposure*. Use of an agricultural pesticide may result, directly or indirectly in pesticide residues in food. These residues are determined by chemical analysis. Data from field studies are evaluated to determine the appropriate level of residue that would not be exceeded if the pesticide were used according to the label use directions.

In examining aggregate exposure, FQPA directs EPA to consider available information concerning exposures from the pesticide residue in food and all other non-occupational exposures. The primary non-food sources of exposure the Agency looks at include drinking water (whether from groundwater or surface water), and exposure through pesticide use in gardens, lawns or buildings (residential and other indoor uses). In evaluating food exposures, EPA takes into account varying consumption patterns of major identifiable subgroups of consumers, including infants and children.

2. *Food*. Tolerances for residues of tebufenozide are currently expressed as benzoic acid, 3,5-dimethyl-1–(1,1-dimethylethyl)-2(4-ethylbenzoyl) hydrazide. Tolerances currently exist for residues on apples at 1.0 ppm (import tolerance) and on walnuts at 0.1 ppm (see 40 CFR 180.482). In addition to this action, a request to establish a tolerance in or on kiwifruit, other petitions are pending for the following tolerances: pome fruit, livestock commodities, pecans, wine grapes (import tolerance), cotton, and the crop subgroups leafy greens, leaf petioles, head and stem Brassica and leafy Brassica greens.

i. *Acute risk*. No appropriate acute dietary endpoint was identified by the Agency. This risk assessment is not required.

ii. *Chronic risk*. For chronic dietary risk assessment, the tolerance values are used and the assumption that all of these crops which are consumed in the U.S. will contain residues at the tolerance level. The theoretical maximum residue contribution (TMRC) using existing and future potential tolerances for tebufenozide on food crops is obtained by multiplying the tolerance level residues (existing and proposed) by the consumption data which estimates the amount of those food products consumed by various population subgroups and assuming that 100% of the food crops grown in the U.S. are treated with tebufenozide. The Theoretical Maximum Residue Contribution (TMRC) from current and future tolerances is calculated using the Dietary Exposure Evaluation Model (Version 5.03b, licensed by Novigen Sciences Inc.) which uses USDA food consumption data from the 1989–1992 survey.

With the current and proposed uses of tebufenozide, the TMRC estimate represents 20.1% of the Reference Dose (RfD) for the U.S. population as a whole. The subgroup with the greatest chronic exposure is non-nursing infants (less than 1 year old), for which the TMRC estimate represents 52.0% of the RfD. Using anticipate residue levels for these crops utilizes 3.38% of the RfD for the U.S. population and 12.0% for non-nursing infants. The chronic dietary risks from these uses do not exceed EPA's level of concern.

3. *Drinking water.* An additional potential source of dietary exposure to residues of pesticides are residues in drinking water. Review of environmental fate data by the Environmental Fate and Effects Division concludes that tebufenozide is moderately persistent to persistent and mobile, and could potentially leach to groundwater and runoff to surface water under certain environmental conditions. However, in terrestrial field dissipation studies, residues of tebufenozide and its soil metabolites showed no downward mobility and remained associated with the upper layers of soil. Foliar

interception (up to 60% of the total dosage applied) by target crops reduces the ground level residues of tebufenozide. There is no established Maximum Concentration Level (MCL) for residues of tebufenozide in drinking water. No drinking water health advisory levels have been established for tebufenozide.

There are no available data to perform a quantitative drinking water risk assessment for tebufenozide at this time. However, in order to mitigate the potential for tebufenozide to leach into groundwater or runoff to surface water, precautionary language has been incorporated into the product label. Also, to the best of our knowledge, previous experience with more persistent and mobile pesticides for which there have been available data to perform quantitative risk assessments have demonstrated that drinking water exposure is typically a small percentage of the total exposure when compared to the total dietary exposure. This observation holds even for pesticides detected in wells and drinking water at levels nearing or exceeding established MCLs. Considering the precautionary language on the label and based on our knowledge of previous experience with persistent chemicals, significant exposure from residues of tebufenozide in drinking water is not anticipated.

4. *Non-dietary exposure.* Tebufenozide is not registered for either indoor or outdoor residential use. Non-occupational exposure to the general population is therefore not expected and not considered in aggregate exposure estimates.

D. Cumulative Effects

The potential for cumulative effects of tebufenozide with other substances that have a common mechanism of toxicity was considered. Tebufenozide belongs to the class of insecticide chemicals known as diacylhydrazines. The only other diacylhydrazine currently registered for non-food crop uses is halofenozide. Tebufenozide and halofenozide both produce a mild, reversible anemia following subchronic/chronic exposure at high doses; however, halofenozide also exhibits other patterns of toxicity (liver toxicity following subchronic exposure and developmental/systemic toxicity following acute exposure) which tebufenozide does not. Given the different spectrum of toxicity produced by tebufenozide, there is no reliable data at the molecular/mechanistic level which would indicate that toxic effects produced by tebufenozide would be cumulative with those of halofenozide (or any other chemical compound).

In addition to the observed differences in mammalian toxicity, tebufenozide also exhibits unique toxicity against target insect pests. Tebufenozide is an agonist of 20–hydroxyecdysone, the insect molting hormone, and interferes with the normal molting process in target lepidopteran species by interacting with ecdysone receptors from those species. Unlike other ecdysone agonists such as halofenozide, tebufenozide does not produces symptoms which may be indicative of systemic toxicity in beetle larvae (Coleopteran species). Tebufenozide has a different spectrum of activity than other ecdysone agonists. In contrast to the other agonists such as halofenozide which act mainly on coleopteran insects, tebufenozide is highly specific for lepidopteran insects.

Based on the overall pattern of toxicity produced by tebufenozide in mammalian and insect systems, the compound's toxicity appears to be distinct from that of other chemicals, including organochlorines, organophosphates, carbamates, pyrethroids, benzoylureas, and other diacylhydrazines. Thus, there is no evidence to date to suggest that cumulative effects of tebufenozide and other chemicals should be considered.

E. Safety Determination

1. *U.S. population*. Using the conservative exposure assumptions described above and taking into account the completeness and reliability of the toxicity data, the dietary exposure to tebufenozide from the current and future tolerances will utilize 20.1% of the RfD for the U.S. population and 52.0% for non-nursing infants under 1 year old. Using anticipate residue levels for these crops utilizes 3.38% of the RfD for the U.S. population and 12.0% for non-nursing infants. EPA generally has no concern for exposures below 100% of the RfD because the RfD represents the level at or below which daily aggregate dietary exposure over a lifetime will not pose appreciable risks to human health. Rohm and Haas concludes that there is a reasonable certainty that no harm will result from aggregate exposure to tebufenozide residues to the U.S. population and non-nursing infants.

2. *Infants and children*. In assessing the potential for additional sensitivity of infants and children to residues of tebufenozide, data from developmental toxicity studies in the rat and rabbit and two 2–generation reproduction studies in the rat are considered. The developmental toxicity studies are designed to evaluate adverse effects on the developing organism resulting from pesticide exposure during prenatal development to one or both parents. Reproduction studies provide information relating to effects from exposure to the pesticide on the reproductive capability of mating animals and data on systemic toxicity. Developmental toxicity was not observed in developmental studies using rats and rabbits. The NOEL for developmental effects in both rats and rabbits was 1,000 mg/kg/day, which is the limit dose for testing in developmental studies.

In the 2–generation reproductive toxicity study in the rat, the reproductive/ developmental toxicity NOEL of 12.1 mg/kg/day was 14–fold higher than the parental (systemic) toxicity NOEL (0.85 mg/kg/day). The reproductive (pup) LOEL of 171.1 mg/kg/day was based on a slight increase in both generations in the number of pregnant females that either did not deliver or had difficulty and had to be sacrificed. In addition, the length of gestation increased and implantation sites decreased significantly in F1 dams. These effects were not replicated at the same dose in a second 2–generation rat reproduction study. In this second study, reproductive effects were not observed at 2,000 ppm (the NOEL equal to 149–195 mg/kg/day) and the NOEL for systemic toxicity was determined to be 25 ppm (1.9–2.3 mg/kg/day).

Because these reproductive effects occurred in the presence of parental (systemic) toxicity and were not replicated at the same doses in a second study, these data do not indicate an increased pre-natal or post-natal sensitivity to children and infants (that infants and children might be more sensitive than adults) to tebufenozide exposure. FFDCA section 408 provides that EPA shall apply an additional safety factor for infants and children in the case of threshold effects to account for pre- and post-natal toxicity and the completeness of the data base unless EPA concludes that a different margin of safety is appropriate. Based on current toxicological data discussed above, an additional uncertainty factor is not warranted and the RfD at 0.018 mg/kg/day is appropriate for assessing aggregate risk to infants and children. Rohm and Haas concludes that there is a reasonable certainty that no harm will occur to infants and children from aggregate exposure to residues of tebufenozide.

F. International Tolerances

There are no approved CODEX maximum residue levels (MRLs) established for residues of tebufenozide.

5. PP 7F4863

EPA has received a pesticide petition (PP 7F4863) from Rohm and Haas Company, 100 Independence Mall West, Philadelphia, PA. 19106–2399, proposing pursuant to section 408(d) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. 346a(d), to amend 40 CFR Part 180 by establishing a tolerance for residues of tebufenozide [benzoic acid, 3,5-dimethyl-, 1–(1,1–dimethylethyl)-2–(4-ethylbenzoyl) hydrazide in or on the raw agricultural commodity sugarcane and sugarcane molasses at 0.3 and 1.0 parts per million (ppm) respectively. EPA has determined that the petition contains data or information regarding the elements set forth in section 408(d)(2) of the FFDCA; however, EPA has not fully evaluated the sufficiency of the submitted data at this time or whether the data supports granting of the petition. Additional data may be needed before EPA rules on the petition.

A. Residue Chemistry

1. *Plant metabolism*. The metabolism of tebufenozide in plants (grapes, apples, rice and sugar beets) is adequately understood for the purposes of these tolerances. The metabolism of tebufenozide in all crops was similar and involves oxidation of the alkyl substituents of the aromatic rings primarily at the benzylic positions. The extent of metabolism and degree of oxidation are a function of time from application to harvest. In all crops, parent compound comprised the majority of the total dosage. None of the metabolites were in excess of 10% of the total dosage. The metabolism of tebufenozide in goats and hens proceeds along the same metabolic pathway as observed in plants. No accumulation of residues in tissues, milk or eggs occurred.

2. *Analytical method*. A validated high performance liquid chromatographic (HPLC) analytical method using ultraviolet (UV) detection is employed for measuring residues of tebufenozide in sugarcane, molasses and refined sugar. The method involves extraction by blending with solvents, purification of the extracts by liquid-liquid partitions and final purification of the residues using solid phase extraction column chromatography. The limit of quantitation of the method for sugarcane, refined sugar and molasses is 0.01 ppm.

B. Toxicological Profile

1. *Acute toxicity*. Tebufenozide has low acute toxicity. Tebufenozide Technical was practically non-toxic by ingestion of a single oral dose in rats and mice (LD_{50} > 5,000 mg/kg) and was practically non-toxic by dermal application (LD_{50} > 5,000 mg/kg). Tebufenozide Technical was not significantly toxic to rats after a 4–hr inhalation exposure with an LC_{50} value of 4.5 mg/L (highest attainable concentration), is not considered to be a primary eye irritant or a skin irritant and is not a dermal sensitizer. An acute neurotoxicity study in rats did not produce any neurotoxic or neuropathologic effects.

2. *Genotoxicty*. Tebufenozide technical was negative (non-mutagenic) in an Ames assay with and without hepatic enzyme activation and in a reverse mutation assay with *E. coli*. Tebufenozide technical was negative in a hypoxanthine guanine phophoribosyl transferase (HGPRT) gene mutation assay using Chinese hamster ovary (CHO) cells in culture when tested with and without hepatic enzyme activation. In isolated rat hepatocytes, tebufenozide technical did not induce unscheduled DNA synthesis (UDS) or repair when tested up to the maximum soluble concentration in culture medium. Tebufenozide did not produce chromosome effects *in vivo* using rat bone marrow cells or *in vitro* using Chinese hamster ovary cells (CHO). On the basis of the results from this battery of tests, it is concluded that tebufenozide is not mutagenic or genotoxic.

3. *Reproductive and developmental toxicity*. —i. No Observable Effect Levels (NOELs) for developmental and maternal toxicity to tebufenozide were established at 1,000 mg/kg/day (Highest Dose Tested) in both the rat and rabbit. No signs of developmental toxicity were exhibited.

ii. In a 2–generation reproduction study in the rat, the reproductive/developmental toxicity NOEL of 12.1 mg/kg/day was 14–fold higher than the parental (systemic) toxicity NOEL 10 ppm 0.85 mg/kg/day. Equivocal reproductive effects were observed only at the 2,000 ppm dose.

iii. In a second rat reproduction study, the equivocal reproductive effects were not observed at 2,000 ppm (the NOEL equal to 149–195 mg/kg/day) and the NOEL for systemic toxicity was determined to be 25 ppm (1.9–2.3 mg/kg/day).

4. *Subchronic toxicity*. —i. The NOEL in a 90–day rat feeding study was 200 ppm (13 mg/kg/day for males, 16 mg/kg/day for females). The lowest-observed-effect-level (LOEL) was 2,000 ppm (133 mg/kg/day for males, 155 mg/kg/day for females). Decreased body weights in males and females was observed at the LOEL of 2,000 ppm. As part of this study, the potential for tebufenozide to produce subchronic neurotoxicity was investigated. Tebufenozide did not produce neurotoxic or neuropathologic effects when administered in the diets of rats for 3 months at concentrations up to and including the limit dose of 20,000 ppm (NOEL = 1,330 mg/kg/day for males, 1,650 mg/kg/day for females).

ii. In a 90–day feeding study with mice, the NOEL was 20 ppm (3.4 and 4.0 mg/kg/day for males and females, respectively). The LOEL was 200 ppm (35.3 and 44.7 mg/kg/day for males and females, respectively). Decreases in body weight gain were noted in male mice at the LOEL of 200 ppm.

iii. A 90–day dog feeding study gave a NOEL of 50 ppm (2.1 mg/kg/day for males and females). The LOEL was 500 ppm (20.1 and 21.4 mg/kg/day for males and females, respectively). At the LOEL, females exhibited a decrease in rate of weight gain and males presented an increased reticulocyte.

iv. A 10–week study was conducted in the dog to examine the reversibility of the effects on hematological parameters that were observed in other dietary studies with the dog. Tebufenozide was administered for 6 weeks in the diet to 4 male dogs at concentrations of either 0 or 1,500 ppm. After the 6th week, the dogs receiving treated feed were switched to the control diet for 4 weeks. Hematological parameters were measured in both groups prior to treatment, at the end of the 6–week treatment, after 2 weeks of recovery on the control diet and after 4 weeks of recovery on the control diet. All hematological parameters in the treated/recovery group were returned to control levels indicating that the effects of tebufenozide on the hemopoietic system are reversible in the dog.

v. In a 28–day dermal toxicity study in the rat, the NOEL was 1,000 mg/kg/day, the highest dose tested. Tebufenozide did not produce toxicity in the rat when administered dermally for 4 weeks at doses up to and including the limit dose of 1,000 mg/kg/day.

5. *Chronic toxicity*. —i. A 1 year feeding study in dogs resulted in decreased red blood cells, hematocrit, and hemoglobin and increased Heinz bodies, reticulocytes, and platelets at the Lowest Observed Effect Level (LOEL) of 8.7 mg/kg/day. The NOEL in this study was 1.8 mg/kg/day.

ii. An 18–month mouse carcinogenicity study showed no signs of carcinogenicity at dosage levels up to and including 1,000 ppm, the highest dose tested.

iii. In a combined rat chronic/oncogenicity study, the NOEL for chronic toxicity was 100 ppm (4.8 and

6.1 mg/kg/day for males and females, respectively) and the LOEL was 1,000 ppm (48 and 61 mg/kg/day for males and females, respectively). No carcinogenicity was observed at the dosage levels up to 2,000 ppm (97 mg/kg/day and 125 mg/kg/day for males and females, respectively).

6. *Animal metabolism*. The adsorption, distribution, excretion and metabolism of tebufenozide in rats was investigated. Tebufenozide is partially absorbed, is rapidly excreted and does not accumulate in tissues. Although tebufenozide is mainly excreted unchanged, a number of polar metabolites were identified. These metabolites are products of oxidation of the benzylic ethyl or methyl side chains of the molecule. These metabolites were detected in plant and other animal (rat, goat, hen) metabolism studies.

7. *Metabolite toxicology*. Common metabolic pathways for tebufenozide have been identified in both plants (grape, apple, rice and sugar beet) and animals (rat, goat, hen). The metabolic pathway common to both plants and animals involves oxidation of the alkyl substituents (ethyl and methyl groups) of the aromatic rings primarily at the benzylic positions. Extensive degradation and elimination of polar metabolites occurs in animals such that residue are unlikely to accumulate in humans or animals exposed to these residues through the diet.

8. *Endocrine disruption*. The toxicology profile of tebufenozide shows no evidence of physiological effects characteristic of the disruption of the hormone estrogen. Based on structure-activity information, tebufenozide is unlikely to exhibit estrogenic activity. Tebufenozide was not active in a direct *in vitro* estrogen binding assay. No indicators of estrogenic or other endocrine effects were observed in mammalian chronic studies or in mammalian and avian reproduction studies. Ecdysone has no known effects in vertebrates. Overall, the weight of evidence provides no indication that tebufenozide has endocrine activity in vertebrates.

C. Aggregate Exposure

1. *Dietary exposure*. Use of an agricultural pesticide may result, directly or indirectly in pesticide residues in food. These residues are determined by chemical analysis. Data from field studies are evaluated to determine the appropriate level of residue that would not be exceeded if the pesticide were used according to the label use directions.

In examining aggregate exposure, FQPA directs EPA to consider available information concerning exposures from the pesticide residue in food and all other non-occupational exposures. The primary non-food sources of exposure the Agency looks at include drinking water (whether from groundwater or surface water), and exposure through pesticide use in gardens, lawns or buildings (residential and other indoor uses). In evaluating food exposures, EPA takes into account varying consumption patterns of major identifiable subgroups of consumers, including infants and children. In examining aggregate exposure, FQPA directs EPA to consider available information concerning exposures from the pesticide residue in food and all other non-occupational exposures. The primary non-food sources of exposure the Agency looks at include drinking water (whether from groundwater or surface water), and exposure through pesticide use in gardens, lawns or buildings (residential and other indoor uses). In evaluating food exposures, EPA takes into account varying consumption patterns of major identifiable subgroups of consumers, including infants and children.

2. *Food*. Tolerances for residues of tebufenozide are currently expressed as benzoic acid, 3,5-dimethyl-1–(1,1-dimethylethyl)-2(4-ethylbenzoyl) hydrazide. Tolerances currently exist for residues on apples at 1.0 ppm (import tolerance) and on walnuts at 0.1 ppm (see 40 CFR 180.482). In addition to this action, a request to establish tolerance in or on sugarcane and sugarcane molasses, other petitions are pending for the following tolerances: pome fruit, livestock commodities, pecans, wine grapes (import tolerance), cotton, and the crop subgroups leafy greens, leaf petioles, head and stem Brassica and leafy Brassica greens and kiwifruit.

i. *Acute risk*. No appropriate acute dietary endpoint was identified by the Agency. This risk assessment is not required.

ii. *Chronic risk*. For chronic dietary risk assessment, the tolerance values are used and the assumption that all of these crops which are consumed in the U.S. will contain residues at the tolerance level. The theoretical maximum residue contribution (TMRC) using existing and future potential tolerances for tebufenozide on food crops is obtained by multiplying the tolerance level residues (existing and proposed) by the consumption data which estimates the amount of those food products consumed by various population subgroups and assuming that 100% of the food crops grown in the U.S. are treated with tebufenozide. The Theoretical Maximum Residue Contribution (TMRC) from current and future tolerances is calculated using the Dietary Exposure Evaluation Model (Version 5.03b, licensed by Novigen Sciences Inc.) which uses USDA food consumption data from the 1989–1992 survey.

With the current and proposed uses of tebufenozide, the TMRC estimate represents 28.9% of the Reference Dose (RfD) for the U.S. population as a whole. The subgroup with the greatest chronic exposure is non-nursing infants (less than 1 year old), for which the TMRC estimate represents 57.0% of the RfD. Using anticipate residue levels for these crops utilizes 5.37% of the RfD for the U.S. population and 13.0% for non-nursing infants. The chronic dietary risks from these uses do not exceed EPA's level of concern.

3. *Drinking water.* An additional potential source of dietary exposure to residues of pesticides are residues in drinking water. Review of environmental fate data by the Environmental Fate and Effects Division concludes that tebufenozide is moderately persistent to persistent and mobile, and could potentially leach to groundwater and runoff to surface water under certain environmental conditions. However, in terrestrial field dissipation studies, residues of tebufenozide and its soil metabolites showed no downward mobility and remained associated with the upper layers of soil. Foliar interception (up to 60% of the total dosage applied) by target crops reduces the ground level residues of tebufenozide. There is no established Maximum Concentration Level (MCL) for residues of tebufenozide in drinking water. No drinking water health advisory levels have been established for tebufenozide. There are no available data to perform a quantitative drinking water risk assessment for tebufenozide at this time. However, in order to mitigate the potential for tebufenozide to leach into groundwater or runoff to surface water, precautionary language has been incorporated into the product label. Also, to the best of our knowledge, previous experience with more persistent and mobile pesticides for which there have been available data to perform quantitative risk assessments have demonstrated that drinking water exposure is typically a small percentage of the total exposure when compared to the total dietary exposure. This observation holds even for pesticides detected in wells and drinking water at levels nearing or exceeding established MCLs. Considering the precautionary language on the label and based on our knowledge of previous experience with persistent chemicals, significant

exposure from residues of tebufenozide in drinking water is not anticipated.

4. *Non-dietary exposure.* Tebufenozide is not registered for either indoor or outdoor residential use. Non-occupational exposure to the general population is therefore not expected and not considered in aggregate exposure estimates.

D. Cumulative Effects

The potential for cumulative effects of tebufenozide with other substances that have a common mechanism of toxicity was considered. Tebufenozide belongs to the class of insecticide chemicals known as diacylhydrazines. The only other diacylhydrazine currently registered for non-food crop uses is halofenozide. Tebufenozide and halofenozide both produce a mild, reversible anemia following subchronic/chronic exposure at high doses; however, halofenozide also exhibits other patterns of toxicity (liver toxicity following subchronic exposure and developmental/systemic toxicity following acute exposure) which tebufenozide does not. Given the different spectrum of toxicity produced by tebufenozide, there is no reliable data at the molecular/mechanistic level which would indicate that toxic effects produced by tebufenozide would be cumulative with those of halofenozide (or any other chemical compound).

In addition to the observed differences in mammalian toxicity, tebufenozide also exhibits unique toxicity against target insect pests. Tebufenozide is an agonist of 20–hydroxyecdysone, the insect molting hormone, and interferes with the normal molting process in target lepidopteran species by interacting with ecdysone receptors from those species. Unlike other ecdysone agonists such as halofenozide, tebufenozide does not produces symptoms which may be indicative of systemic toxicity in beetle larvae (Coleopteran species). Tebufenozide has a different spectrum of activity than other ecdysone agonists. In contrast to the other agonists such as halofenozide which act mainly on coleopteran insects, tebufenozide is highly specific for lepidopteran insects.

Based on the overall pattern of toxicity produced by tebufenozide in mammalian and insect systems, the compound's toxicity appears to be distinct from that of other chemicals, including organochlorines, organophosphates, carbamates, pyrethroids, benzoylureas, and other diacylhydrazines. Thus, there is no evidence to date to suggest that cumulative effects of tebufenozide and other chemicals should be considered.

E. Safety Determination

1. *U.S. population.*Using the conservative exposure assumptions described above and taking into account the completeness and reliability of the toxicity data, the dietary exposure to tebufenozide from the current and future tolerances will utilize 28.9% of the RfD for the U.S. population and 57.0% for non-nursing infants under 1 year old. Using anticipate residue levels for these crops utilizes 5.37% of the RfD for the U.S. population and 13.0% for non-nursing infants. EPA generally has no concern for exposures below 100% of the RfD because the RfD represents the level at or below which daily aggregate dietary exposure over a lifetime will not pose appreciable risks to human health. Rohm and Haas concludes that there is a reasonable certainty that no harm will result from aggregate exposure to tebufenozide residues to the U.S. population and non-nursing infants.

2. *Infants and children.* In assessing the potential for additional sensitivity of infants and children to residues of tebufenozide, data from developmental toxicity studies in the rat and rabbit and two 2–generation reproduction studies in the rat are considered. The developmental toxicity studies are designed to evaluate adverse effects on the developing organism resulting from pesticide exposure during prenatal development to one or both parents. Reproduction studies provide information relating to effects from exposure to the pesticide on the reproductive capability of mating animals and data on systemic toxicity. Developmental toxicity was not observed in developmental studies using rats and rabbits. The NOEL for developmental effects in both rats and rabbits was 1,000 mg/kg/day, which is the limit dose for testing in developmental studies.

In the 2–generation reproductive toxicity study in the rat, the reproductive/ developmental toxicity NOEL of 12.1 mg/kg/day was 14–fold higher than the parental (systemic) toxicity NOEL (0.85 mg/kg/day). The reproductive (pup) LOEL of 171.1 mg/kg/day was based on a slight increase in both generations in the number of pregnant females that either did not deliver or had difficulty and had to be sacrificed. In addition, the length of gestation increased and implantation sites decreased significantly in F1 dams. These effects were not replicated at the same dose in a second 2–generation rat reproduction study. In this second study, reproductive effects were not observed at 2,000 ppm (the NOEL equal to 149–195 mg/kg/day) and the NOEL for systemic toxicity was determined to be 25 ppm (1.9–2.3 mg/kg/day).

Because these reproductive effects occurred in the presence of parental (systemic) toxicity and were not replicated at the same doses in a second study, these data do not indicate an increased pre-natal or post-natal sensitivity to children and infants (that infants and children might be more sensitive than adults) to tebufenozide exposure. FFDCA section 408 provides that EPA shall apply an additional safety factor for infants and children in the case of threshold effects to account for pre- and post-natal toxicity and the completeness of the data base unless EPA concludes that a different margin of safety is appropriate. Based on current toxicological data discussed above, an additional uncertainty factor is not warranted and the RfD at 0.018 mg/kg/day is appropriate for assessing aggregate risk to infants and children. Rohm and Haas concludes that there is a reasonable certainty that no harm will occur to infants and children from aggregate exposure to residues of tebufenozide.

F. International Tolerances

There are no approved CODEX maximum residue levels (MRLs) established for residues of tebufenozide.

6. PP 7F4869

EPA has received PP 7F4869 from Rohm and Haas Company, 100 Independence Mall West, Philadelphia, PA. 19106–2399, proposing pursuant to section 408(d) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. 346a(d), to amend 40 CFR Part 180 by establishing a tolerance for residues of tebufenozide [benzoic acid, 3,5-dimethyl-, 1–(1,1-dimethylethyl)-2–(4-ethylbenzoyl) hydrazide in or on the raw agricultural commodity fruiting vegetables (except cucurbits) at 0.8 parts per million (ppm). EPA has determined that the petition contains data or information regarding the elements set forth in section 408(d)(2) of the FFDCA; however, EPA has not fully evaluated the sufficiency of the submitted data at this time or whether the data supports granting of the petition. Additional data may be needed before EPA rules on the petition.

A. Residue Chemistry

1. *Plant metabolism.* The metabolism of tebufenozide in plants (grapes, apples, rice and sugar beets) is adequately understood for the purposes of these tolerances. The metabolism of tebufenozide in all crops was similar and involves oxidation of the alkyl

substituents of the aromatic rings primarily at the benzylic positions. The extent of metabolism and degree of oxidation are a function of time from application to harvest. In all crops, parent compound comprised the majority of the total dosage. None of the metabolites were in excess of 10% of the total dosage. The metabolism of tebufenozide in goats and hens proceeds along the same metabolic pathway as observed in plants. No accumulation of residues in tissues, milk or eggs occurred.

2. *Analytical method*. A validated high performance liquid chromatographic (HPLC) analytical method using ultraviolet (UV) detection is employed for measuring residues of tebufenozide in tomatoes, peppers and tomato processed fractions. The method involves extraction by blending with solvents, purification of the extracts by liquid-liquid partitions and final purification of the residues using solid phase extraction column chromatography. The limit of quantitation of the method for all matrices is 0.02 ppm.

B. Toxicological Profile

1. *Acute toxicity*. Tebufenozide has low acute toxicity. Tebufenozide Technical was practically non-toxic by ingestion of a single oral dose in rats and mice (LD_{50} > 5,000 mg/kg) and was practically non-toxic by dermal application (LD_{50} > 5,000 mg/kg). Tebufenozide Technical was not significantly toxic to rats after a 4–hr inhalation exposure with an LC_{50} value of 4.5 mg/L (highest attainable concentration), is not considered to be a primary eye irritant or a skin irritant and is not a dermal sensitizer. An acute neurotoxicity study in rats did not produce any neurotoxic or neuropathologic effects.

2. *Genotoxicty*. Tebufenozide technical was negative (non-mutagenic) in an Ames assay with and without hepatic enzyme activation and in a reverse mutation assay with *E. coli*. Tebufenozide technical was negative in a hypoxanthine guanine phophoribosyl transferase (HGPRT) gene mutation assay using Chinese hamster ovary (CHO) cells in culture when tested with and without hepatic enzyme activation. In isolated rat hepatocytes, tebufenozide technical did not induce unscheduled DNA synthesis (UDS) or repair when tested up to the maximum soluble concentration in culture medium. Tebufenozide did not produce chromosome effects *in vivo* using rat bone marrow cells or *in vitro* using Chinese hamster ovary cells (CHO). On the basis of the results from this battery of tests, it is concluded that tebufenozide is not mutagenic or genotoxic.

3. *Reproductive and developmental toxicity*. —i. No Observable Effect Levels (NOELs) for developmental and maternal toxicity to tebufenozide were established at 1,000 mg/kg/day (Highest Dose Tested) in both the rat and rabbit. No signs of developmental toxicity were exhibited.

ii. In a 2–generation reproduction study in the rat, the reproductive/developmental toxicity NOEL of 12.1 mg/kg/day was 14–fold higher than the parental (systemic) toxicity NOEL 10 ppm 0.85 mg/kg/day. Equivocal reproductive effects were observed only at the 2,000 ppm dose.

iii. In a second rat reproduction study, the equivocal reproductive effects were not observed at 2,000 ppm (the NOEL equal to 149–195 mg/kg/day) and the NOEL for systemic toxicity was determined to be 25 ppm (1.9–2.3 mg/kg/day).

4. *Subchronic toxicity*. —i. The NOEL in a 90–day rat feeding study was 200 ppm (13 mg/kg/day for males, 16 mg/kg/day for females). The lowest-observable-effect-level (LOEL) was 2,000 ppm (133 mg/kg/day for males, 155 mg/kg/day for females). Decreased body weights in males and females was observed at the LOEL of 2,000 ppm. As part of this study, the potential for tebufenozide to produce subchronic neurotoxicity was investigated. Tebufenozide did not produce neurotoxic or neuropathologic effects when administered in the diets of rats for 3 months at concentrations up to and including the limit dose of 20,000 ppm (NOEL = 1,330 mg/kg/day for males, 1,650 mg/kg/day for females).

ii. In a 90–day feeding study with mice, the NOEL was 20 ppm (3.4 and 4.0 mg/kg/day for males and females, respectively). The LOEL was 200 ppm (35.3 and 44.7 mg/kg/day for males and females, respectively). Decreases in body weight gain were noted in male mice at the LOEL of 200 ppm.

iii. A 90–day dog feeding study gave a NOEL of 50 ppm (2.1 mg/kg/day for males and females). The LOEL was 500 ppm (20.1 and 21.4 mg/kg/day for males and females, respectively). At the LOEL, females exhibited a decrease in rate of weight gain and males presented an increased reticulocyte.

iv. A 10–week study was conducted in the dog to examine the reversibility of the effects on hematological parameters that were observed in other dietary studies with the dog. Tebufenozide was administered for 6 weeks in the diet to 4 male dogs at concentrations of either 0 or 1,500 ppm. After the 6th week, the dogs receiving treated feed were switched to the control diet for 4 weeks. Hematological parameters were measured in both groups prior to treatment, at the end of the 6-week treatment, after 2 weeks of recovery on the control diet and after 4 weeks of recovery on the control diet. All hematological parameters in the treated/recovery group were returned to control levels indicating that the effects of tebufenozide on the hemopoietic system are reversible in the dog.

v. In a 28–day dermal toxicity study in the rat, the NOEL was 1,000 mg/kg/day, the highest dose tested. Tebufenozide did not produce toxicity in the rat when administered dermally for 4 weeks at doses up to and including the limit dose of 1,000 mg/kg/day.

5. *Chronic toxicity*. —i. A 1 year feeding study in dogs resulted in decreased red blood cells, hematocrit, and hemoglobin and increased Heinz bodies, reticulocytes, and platelets at the Lowest Observed Effect Level (LOEL) of 8.7 mg/kg/day. The NOEL in this study was 1.8 mg/kg/day.

ii. An 18–month mouse carcinogenicity study showed no signs of carcinogenicity at dosage levels up to and including 1,000 ppm, the highest dose tested.

iii. In a combined rat chronic/oncogenicity study, the NOEL for chronic toxicity was 100 ppm (4.8 and 6.1 mg/kg/day for males and females, respectively) and the LOEL was 1,000 ppm (48 and 61 mg/kg/day for males and females, respectively). No carcinogenicity was observed at the dosage levels up to 2,000 ppm (97 mg/kg/day and 125 mg/kg/day for males and females, respectively).

6. *Animal metabolism*. The adsorption, distribution, excretion and metabolism of tebufenozide in rats was investigated. Tebufenozide is partially absorbed, is rapidly excreted and does not accumulate in tissues. Although tebufenozide is mainly excreted unchanged, a number of polar metabolites were identified. These metabolites are products of oxidation of the benzylic ethyl or methyl side chains of the molecule. These metabolites were detected in plant and other animal (rat, goat, hen) metabolism studies.

7. *Metabolite toxicology*. Common metabolic pathways for tebufenozide have been identified in both plants (grape, apple, rice and sugar beet) and animals (rat, goat, hen). The metabolic pathway common to both plants and animals involves oxidation of the alkyl substituents (ethyl and methyl groups) of the aromatic rings primarily at the benzylic positions. Extensive degradation and elimination of polar metabolites occurs in animals such that

residue are unlikely to accumulate in humans or animals exposed to these residues through the diet.

8. *Endocrine disruption*. The toxicology profile of tebufenozide shows no evidence of physiological effects characteristic of the disruption of the hormone estrogen. Based on structure-activity information, tebufenozide is unlikely to exhibit estrogenic activity. Tebufenozide was not active in a direct *in vitro* estrogen binding assay. No indicators of estrogenic or other endocrine effects were observed in mammalian chronic studies or in mammalian and avian reproduction studies. Ecdysone has no known effects in vertebrates. Overall, the weight of evidence provides no indication that tebufenozide has endocrine activity in vertebrates.

C. Aggregate Exposure

1. *Dietary exposure*. Use of an agricultural pesticide may result, directly or indirectly in pesticide residues in food. These residues are determined by chemical analysis. Data from field studies are evaluated to determine the appropriate level of residue that would not be exceeded if the pesticide were used according to the label use directions.

In examining aggregate exposure, FQPA directs EPA to consider available information concerning exposures from the pesticide residue in food and all other non-occupational exposures. The primary non-food sources of exposure the Agency looks at include drinking water (whether from groundwater or surface water), and exposure through pesticide use in gardens, lawns or buildings (residential and other indoor uses). In evaluating food exposures, EPA takes into account varying consumption patterns of major identifiable subgroups of consumers, including infants and children.

2. *Food*. Tolerances for residues of tebufenozide are currently expressed as benzoic acid, 3,5-dimethyl-1–(1,1-dimethylethyl)-2(4-ethylbenzoyl) hydrazide. Tolerances currently exist for residues on apples at 1.0 ppm (import tolerance) and on walnuts at 0.1 ppm (see 40 CFR 180.482). In addition to this action, a request to establish a tolerance in or on the crop group fruiting vegetables (except cucurbits), other petitions are pending for the following tolerances: pome fruit, livestock commodities, pecans, wine grapes (import tolerance), cotton, and the crop subgroups leafy greens, leaf petioles, head and stem Brassica and leafy Brassica greens, kiwifruit (import tolerance) and sugarcane.

i. *Acute risk. No appropriate acute dietary endpoint was identified by the Agency. This risk assessment is not required.*

ii. *Chronic risk*. For chronic dietary risk assessment, the tolerance values are used and the assumption that all of these crops which are consumed in the U.S. will contain residues at the tolerance level. The theoretical maximum residue contribution (TMRC) using existing and future potential tolerances for tebufenozide on food crops is obtained by multiplying the tolerance level residues (existing and proposed) by the consumption data which estimates the amount of those food products consumed by various population subgroups and assuming that 100% of the food crops grown in the U.S. are treated with tebufenozide. The Theoretical Maximum Residue Contribution (TMRC) from current and future tolerances is calculated using the Dietary Exposure Evaluation Model (Version 5.03b, licensed by Novigen Sciences Inc.) which uses USDA food consumption data from the 1989–1992 survey.

With the current and proposed uses of tebufenozide, the TMRC estimate represents 28.9% of the Reference Dose (RfD) for the U.S. population as a whole. The subgroup with the greatest chronic exposure is non-nursing infants (less than 1 year old), for which the TMRC estimate represents 57.0% of the RfD. Using anticipate residue levels for these crops utilizes 5.37% of the RfD for the U.S. population and 13.0% for non-nursing infants. The chronic dietary risks from these uses do not exceed EPA's level of concern.

3. *Drinking water*. An additional potential source of dietary exposure to residues of pesticides are residues in drinking water. Review of environmental fate data by the Environmental Fate and Effects Division concludes that tebufenozide is moderately persistent to persistent and mobile, and could potentially leach to groundwater and runoff to surface water under certain environmental conditions. However, in terrestrial field dissipation studies, residues of tebufenozide and its soil metabolites showed no downward mobility and remained associated with the upper layers of soil. Foliar interception (up to 60% of the total dosage applied) by target crops reduces the ground level residues of tebufenozide. There is no established Maximum Concentration Level (MCL) for residues of tebufenozide in drinking water. No drinking water health advisory levels have been established for tebufenozide.

There are no available data to perform a quantitative drinking water risk assessment for tebufenozide at this time. However, in order to mitigate the potential for tebufenozide to leach into groundwater or runoff to surface water, precautionary language has been incorporated into the product label.

Also, to the best of our knowledge, previous experience with more persistent and mobile pesticides for which there have been available data to perform quantitative risk assessments have demonstrated that drinking water exposure is typically a small percentage of the total exposure when compared to the total dietary exposure. This observation holds even for pesticides detected in wells and drinking water at levels nearing or exceeding established MCLs. Considering the precautionary language on the label and based on our knowledge of previous experience with persistent chemicals, significant exposure from residues of tebufenozide in drinking water is not anticipated.

4. *Non-dietary exposure*. Tebufenozide is not registered for either indoor or outdoor residential use. Non-occupational exposure to the general population is therefore not expected and not considered in aggregate exposure estimates.

D. Cumulative Effects

The potential for cumulative effects of tebufenozide with other substances that have a common mechanism of toxicity was considered. Tebufenozide belongs to the class of insecticide chemicals known as diacylhydrazines. The only other diacylhydrazine currently registered for non-food crop uses is halofenozide. Tebufenozide and halofenozide both produce a mild, reversible anemia following subchronic/chronic exposure at high doses; however, halofenozide also exhibits other patterns of toxicity (liver toxicity following subchronic exposure and developmental/systemic toxicity following acute exposure) which tebufenozide does not. Given the different spectrum of toxicity produced by tebufenozide, there is no reliable data at the molecular/mechanistic level which would indicate that toxic effects produced by tebufenozide would be cumulative with those of halofenozide (or any other chemical compound).

In addition to the observed differences in mammalian toxicity, tebufenozide also exhibits unique toxicity against target insect pests. Tebufenozide is an agonist of 20–hydroxyecdysone, the insect molting hormone, and interferes with the normal molting process in target lepidopteran species by interacting with ecdysone

receptors from those species. Unlike other ecdysone agonists such as halofenozide, tebufenozide does not produces symptoms which may be indicative of systemic toxicity in beetle larvae (Coleopteran species). Tebufenozide has a different spectrum of activity than other ecdysone agonists. In contrast to the other agonists such as halofenozide which act mainly on coleopteran insects, tebufenozide is highly specific for lepidopteran insects.

Based on the overall pattern of toxicity produced by tebufenozide in mammalian and insect systems, the compound's toxicity appears to be distinct from that of other chemicals, including organochlorines, organophosphates, carbamates, pyrethroids, benzoylureas, and other diacylhydrazines. Thus, there is no evidence to date to suggest that cumulative effects of tebufenozide and other chemicals should be considered.

E. Safety Determination

1. *U.S. population*. Using the conservative exposure assumptions described above and taking into account the completeness and reliability of the toxicity data, the dietary exposure to tebufenozide from the current and future tolerances will utilize 28.9% of the RfD for the U.S. population and 57.0% for non-nursing infants under 1 year old. Using anticipate residue levels for these crops utilizes 5.37% of the RfD for the U.S. population and 13.0% for non-nursing infants. EPA generally has no concern for exposures below 100% of the RfD because the RfD represents the level at or below which daily aggregate dietary exposure over a lifetime will not pose appreciable risks to human health. Rohm and Haas concludes that there is a reasonable certainty that no harm will result from aggregate exposure to tebufenozide residues to the U.S. population and non-nursing infants.

2. *Infants and children*. In assessing the potential for additional sensitivity of infants and children to residues of tebufenozide, data from developmental toxicity studies in the rat and rabbit and two 2–generation reproduction studies in the rat are considered. The developmental toxicity studies are designed to evaluate adverse effects on the developing organism resulting from pesticide exposure during prenatal development to one or both parents. Reproduction studies provide information relating to effects from exposure to the pesticide on the reproductive capability of mating animals and data on systemic toxicity. Developmental toxicity was not observed in developmental studies using rats and rabbits. The NOEL for developmental effects in both rats and rabbits was 1,000 mg/kg/day, which is the limit dose for testing in developmental studies.

In the 2–generation reproductive toxicity study in the rat, the reproductive/ developmental toxicity NOEL of 12.1 mg/kg/day was 14–fold higher than the parental (systemic) toxicity NOEL (0.85 mg/kg/day). The reproductive (pup) LOEL of 171.1 mg/kg/day was based on a slight increase in both generations in the number of pregnant females that either did not deliver or had difficulty and had to be sacrificed. In addition, the length of gestation increased and implantation sites decreased significantly in F1 dams. These effects were not replicated at the same dose in a second 2–generation rat reproduction study. In this second study, reproductive effects were not observed at 2,000 ppm (the NOEL equal to 149–195 mg/kg/day) and the NOEL for systemic toxicity was determined to be 25 ppm (1.9–2.3 mg/kg/day).

Because these reproductive effects occurred in the presence of parental (systemic) toxicity and were not replicated at the same doses in a second study, these data do not indicate an increased pre-natal or post-natal sensitivity to children and infants (that infants and children might be more sensitive than adults) to tebufenozide exposure. FFDCA section 408 provides that EPA shall apply an additional safety factor for infants and children in the case of threshold effects to account for pre- and post-natal toxicity and the completeness of the data base unless EPA concludes that a different margin of safety is appropriate. Based on current toxicological data discussed above, an additional uncertainty factor is not warranted and the RfD at 0.018 mg/kg/day is appropriate for assessing aggregate risk to infants and children. Rohm and Haas concludes that there is a reasonable certainty that no harm will occur to infants and children from aggregate exposure to residues of tebufenozide.

F. International Tolerances

There are no approved CODEX Maximum Residue Levels (MRLs) established for residues of tebufenozide.

[FR Doc. 98–21747 Filed 8–18–98; 8:45 am]

BILLING CODE 6560–50–F

FEDERAL COMMUNICATIONS COMMISSION

[Report No. AUC–98–21–A (Auction No. 21); DA 98–1616]

Location and Monitoring Service Spectrum Auction Scheduled For December 15, 1998; Comment Sought on Reserve Prices or Minimum Opening Bids and Other Auction Procedural Issues

AGENCY: Federal Communications Commission.

ACTION: Notice; seeking comment.

SUMMARY: The Commission announces the auction of 528 multilateration Location and Monitoring Service licenses scheduled for December 15, 1998, and seeks comment on a proposed formula for calculating minimum opening bids and other auction procedural issues.

DATES: Comments are due on or before September 2, 1998. Reply comments are due on or before September 9, 1998.

ADDRESSES: To file formally, parties must submit an original and four copies to the Office of the Secretary, Federal Communications Commission, Room 222, 1919 M Street N.W., Washington, D.C. 20554. In addition, parties must submit one copy to Amy Zoslov, Chief, Auctions and Industry Analysis Division, Wireless Telecommunications Bureau, Federal Communications Commission, Room 5202, 2025 M Street N.W., Washington, D.C. 20554. Comments and reply comments will be available for public inspection during regular business hours in the FCC Public Reference Room, Room 239, 1919 M Street N.W., Washington, D.C. 20554.

FOR FURTHER INFORMATION CONTACT: Kathy Garland, Bob Reagle or Kenneth Burnley, Auctions and Industry Analysis Division, Wireless Telecommunications Bureau, at (202) 418–0660.

SUPPLEMENTARY INFORMATION: This public notice was released on August 13, 1998 and is available in its entirety for inspection and copying during normal business hours in the FCC Reference Center (Room 239), 1919 M Street, N.W., Washington, D.C., and also may be purchased from the Commission's copy contractor, International Transcription Services, (202) 857–3800, fax (202) 857–3805, 1231 20th Street, N.W., Washington, D.C. 20036.

Synopsis of the Public Notice

1. By this Public Notice, the Wireless Telecommunications Bureau (''Bureau'') announces the auction of 528